The Utilization of Laboratory Results for the Diagnosis of Blood Disorders with Corvid Software

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Hematology and Blood Disorders

- Blood Disorders can be categorized by White Blood Cell (WBC),Red Blood Cell (RBC), and platelet disorders.
- Patients that enter the clinical setting with these disorders can appear with a variety of symptoms, such as fatigue, pale skin, sweats, weight-loss, fever, or bruising.
- Although there are a number of symptoms that can indicate a blood disorder, the diagnosis of these conditions are almost completely reliant on the patient's blood test results.
- The most important test performed for this purpose in the laboratory is known as the Complete Blood Count, or the CBC.

What is a CBC?

- A complete blood count (CBC) takes a complete measure of the contents of a patient's blood, including their red blood cells, white blood cells, and platelets.
- Oftentimes, if the CBC is flagged as abnormal, a laboratory technologist will prepare a blood smear to manually observe the size, shape, and amount of blood cells using a microscope.
- A CBC can be ordered as a routine screening, ordered if patients have a symptom of a blood disorder (weight-loss, bruising, fatigue, pallor, splenomegaly), or to determine the extent of blood loss.

Parameters in the CBC and their meaning:

- **White Blood Cells:** increase in leukemias, infections, or stress. Decrease in bone marrow disorders or destruction in bloodstream
- **Red Blood cells**: increase in RBCs due to uncontrolled production in bone marrow, plasma loss, or polycythemia. Decreases in anemia: caused by destruction of bone marrow, blood loss, and vitamin deficiency
  - MCV: mean red blood cell volume (80-100 fL)- indicates average size of red blood cells
  - MCH: mean cell hemoglobin (26-32 pg): indicates average hemoglobin per cell
  - MCHC: mean cell hemoglobin concentration (32-36 g/dL)
  - Red Cell Distribution (RDW): variance of red blood cell size in sample (11.5%-14.5%)

Parameters in the CBC and their meanings (continued):

- **Reticulocytes:** immature red blood cells. There are different reference ranges for different ages:
  - An increased production of reticulocytes indicates

  Either a response to blood loss or a possible leukemia depending on how immature the reticulocytes are.

	Visual Retics %
Adults (males and females)	0.5-2.5
Children (1-3 years)	0.5-1.5
Newborns (0-1 day)	1.5-5.8

Source: Rodak's Hematology: Clinical Principles and Applications, 5th ed. Keohane.

- **Platelets:** Increase in platelets due to secondary blood disorders, decreased in consumption of platelets or lack of production in bone marrow

Red Blood Cell Disorders and their Lab Findings:

- Red blood cell disorders, particularly anemias, are very easily diagnosed and classified based on CBC findings: anemias are classified based on macrocytic, microcytic, and normocytic anemias, which are the size of the RBCs, dependent on CBC parameters such as MCV and RDW.
- Anemias are defined as low oxygen-carrying capacity in the blood, characterized by low hemoglobin values.
- This can be caused by lack of iron, vitamin deficiency, anemias caused by chronic disease, lack of iron absorption, lead poisoning, and through thalassemia (hemoglobin disorder).

Manual Cell Counts

- There are many different white blood cells, each of them with different purposes.
- When a CBC shows increased white blood cells, a cell count is often performed to see the predominating white blood cells, as an increase in particular types can have different clinical indications:
- Neutrophils (40-60%): Increase in neutrophils can be caused by: stress, fever, exercise, cortisone therapy, infections, inflammation, and malignancies
    - Decreased neutrophils caused by: bone marrow failure, drugs, vitamin deficiency, overwhelming infection, hemodialysis, and autoimmune disorders.

White Blood Cell Disorders and their Lab Findings:

- Lymphocytes (20-40%): increased due to viral/bacterial infections, acute leukemias, etc. and decreased due to radiation and autoimmune disorders.
- Monocytes (2-8%): increased due to tuberculosis, subacute bacterial endocarditis, syphilis, parasitic and rickettsial infections, recovery phase of acute infections, and some leukemias
- Eosinophils (1-4%): increase caused by allergic reactions, parasitic infections, autoimmune disorders, and chronic myelogenous leukemia
- Basophils (0.5-1%): increase caused by hypothyroid states, ulcerative colitis, and chronic mylogenous leukemia
- Leukemias can be suspected with just a simple CBC and divided into acute or chronic diseases. Further tests are needed to determine to true cause of the leukemia.

Reference Ranges of a Normal CBC and Critical Values:

Assay	Adult Male	Adult Female	Newborn (0-1d)	Children (1-3y)	SI Units	Common Units
RBC	4.60-6.00	4.00-5.40	4.10-6.10	3.40-5.20	x 10^{12}/L	x 10^{6}/µl
HGB (Hb)	14.0-18.0 (140-180)	12.-15.0 (120-150)	16.5-21.5	9.6-15.6 (96-156)	(g/L)	g/dL
HCT	40-54 (.40-.54)	35-49 (.35-.49)	48-68	38-48	(L/L)	%
MCV	80-100	80-100	95-125	78-94	fL	fL
MCH	26-32	26-32	30-42	23-31	pg	pg
MCHC	32-36	32-36	30-34	32-36	g/dL	%
RDW	11.5-14.5	11.5-14.5	*	11.5-14.5	%	%
Retics (manual)	0.5-1.5	0.5-1.5	1.5-5.8	0.5-1.5	x10^{9}/L	x10^{3} / µl
NRBCs	0	0	2-24	0	/ 100 WBC	/100 WBC
WBC	4.5-11.5	4.5-11.5	9.0-37.0	5.5-17.5	x 10^{9}/L	x 10^{9}/L
PLT's	150-450	150-450		150-450	x10^{9}/L	x10^{3} / µl

Source: Rodak's Hematology: Clinical Principles and Applications, 5th ed. Keohane.

These are simple reference ranges and critical values established by the literature over time that will allow us to flag any sort of abnormal result outside of these ranges as a possible blood disorder.

Critical Values - Examples

Procedure	Conventional	SI Units
WBC	<2.0 or >30.0 x 10^{3}/µL	<2.0 or >30.0 x 10^{9}/L
Hemoglobin	<7.0 or >20.0g/dL	<70 or >200 g/L
Hematocrit	<20% or >60%	<0.20 or >0.60 L/L
Platelet	<40.0 or >1000 x 10^{3}/µL	<40.0 or >1000 x 10^{9}/L

Each lab establishes it own critical values in consultation with the clinicians

Source: Rodak's Hematology: Clinical Principles and Applications, 5th ed. Keohane.

Importance of Streamlining Blood Disorder Diagnoses:

- The background information given in previous slides shows that there are a large variety of blood disorders that can be indicated by a complete blood count
- Because there are so many different types of cells in the blood with distinct characteristics and a large variety of causes for clinical findings in a lab report, it is important to have a CDSS that can sort through the clinical findings and guide physicians through the ruling out and further testing of various diseases
- Streamlining the process of diagnosing blood disorders will save the doctor time in going through the data, as well as reducing the costs of redundant tests that were not needed to get to the diagnosis. This is optimal for the patient's recovery.

Using Corvid to Aid in CBC Interpretation

- Corvid is an expert system that uses rules to help make decisions for the user, in this case, would allow one to use rules from the results of the CBC to help us determine a diagnosis.
- As a medical technologist, I understand the importance of these laboratory results that are released to physicians, and therefore can consider myself an “expert” which aids in the construction of an expert, rule-based system.
- Creating rules will allow the system to come up with quick decisions of the next step taken when determining a disease.

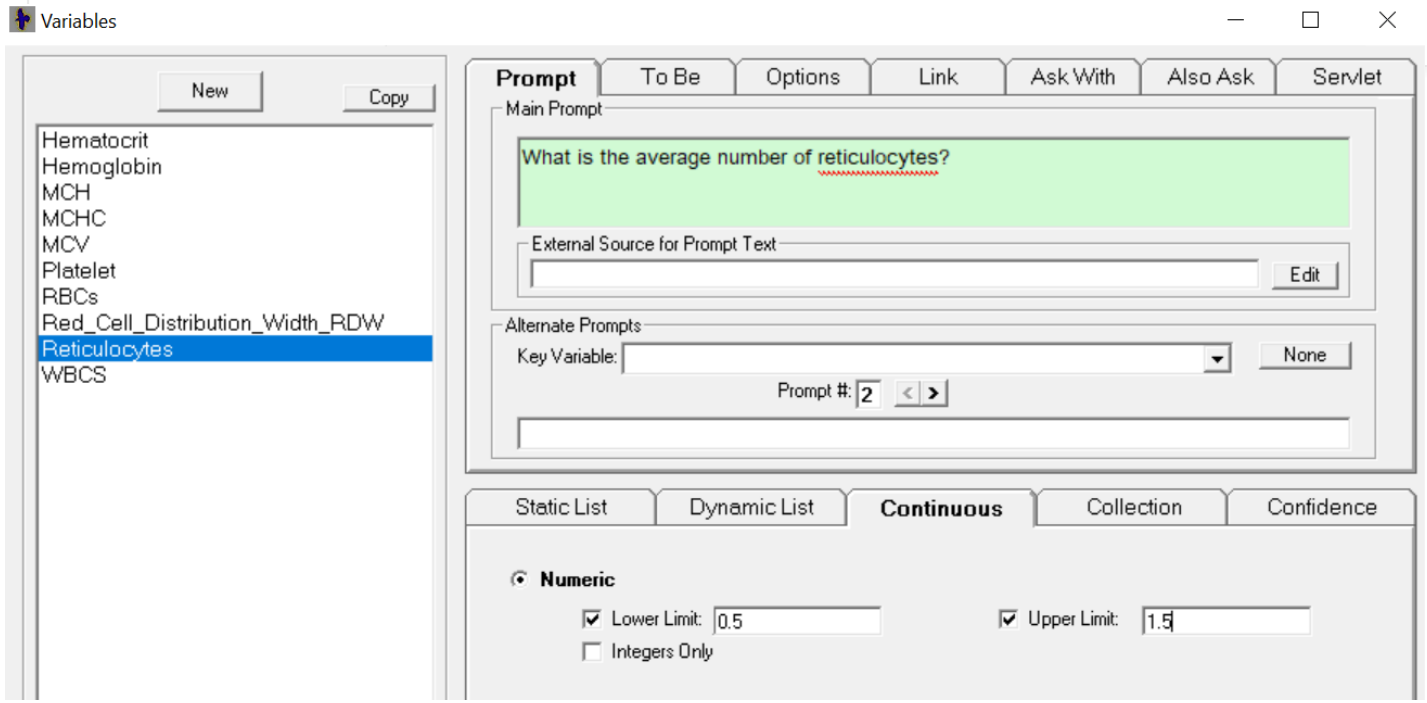
Goals with Corvid Software:

- The software we are developing will:
  - Ask for CBC values starting with each important assay
  - Ask for symptoms the patient may have that indicates blood disorders
  - Use a rule-based decision tree to come up with the best probable diagnosis
  - Will provide the physician with further tests to perform in order to confirm the diagnosis and possible alternatives if the further test rules out the original diagnosis

Forward Chaining

- Forward chaining is an approach used in rule-based expert systems that is utilized in this project for the diagnosis of blood disorders
- Forward-chaining is data-driven, which means that we use data and facts to get towards our goal, which is finding out a diagnosis.
- Because laboratory results are considered bits of “data,” forward chaining is perfect in this scenario to help guide physicians towards the correct blood disorder diagnosis.

Corvid Process- Variables

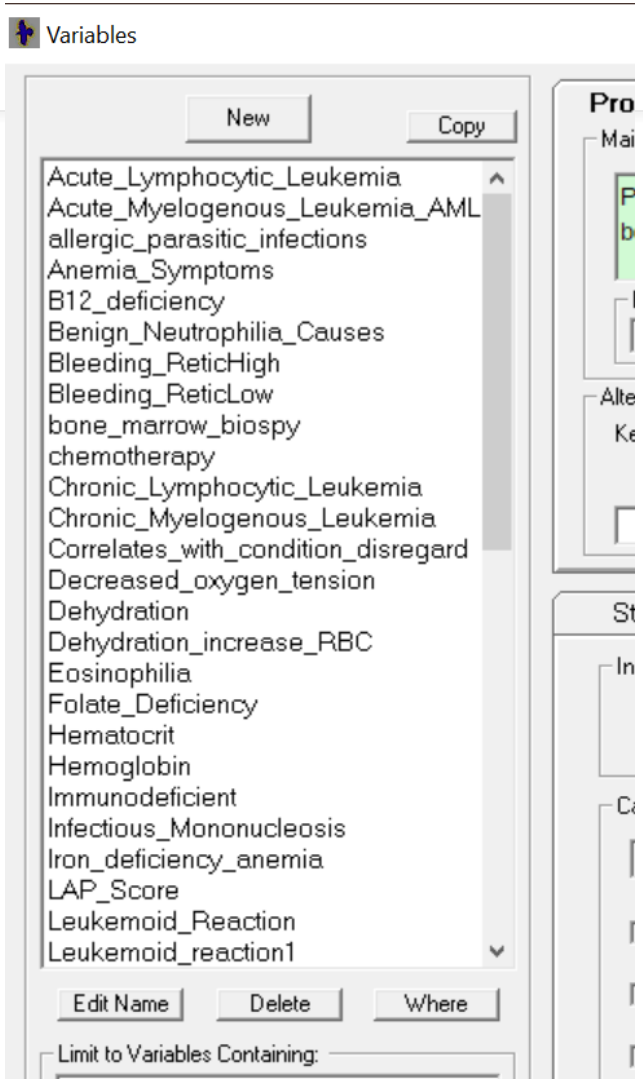


First, I established all the variables in the CBC as numerical variables in CORVID. I documented their lower and upper limits as the reference ranges so that if there is abnormal values, it can easily be detected by the software.

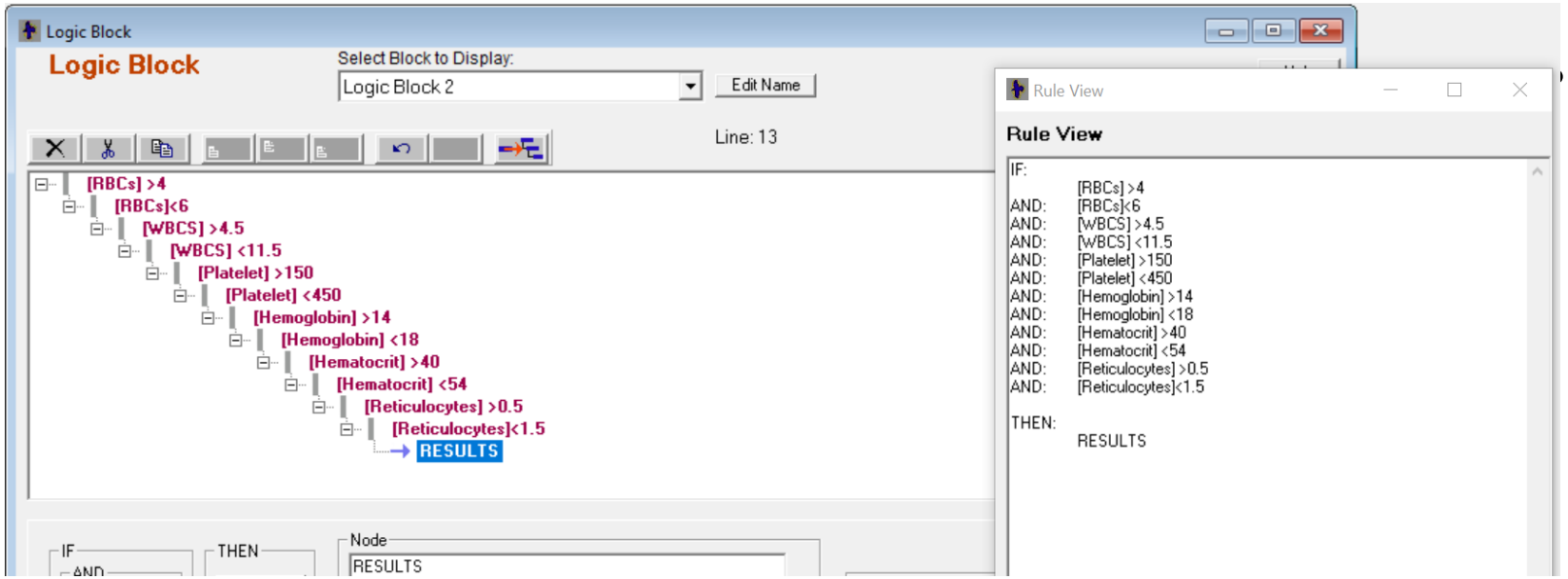
- Note: To establish a standard reference range, we are building the system with the assumption that all of our patients are greater than 4 years old. If they were less than that, the physician can look at literature to establish the reference range for a child less than 4.

Corvid Process-Variables (After)

- After adding all my further questions and confidence variables for my results, I went from 9 variables in my CBC to over 52 variables!
- For simplification purposes, I focused on white and red blood cell disorders, and stopped my CDSS at the point where the physician would need to do further testing involving the bone marrow, iron panels, etc.
- Had I kept going with every single test for every single disorder, this CORVID project would easily have had hundreds of variables. The purpose of this project is to create a preliminary CDSS so the doctor can be in the right direction in terms of what tests to order in the first place.



Corvid Process- Normal Patient

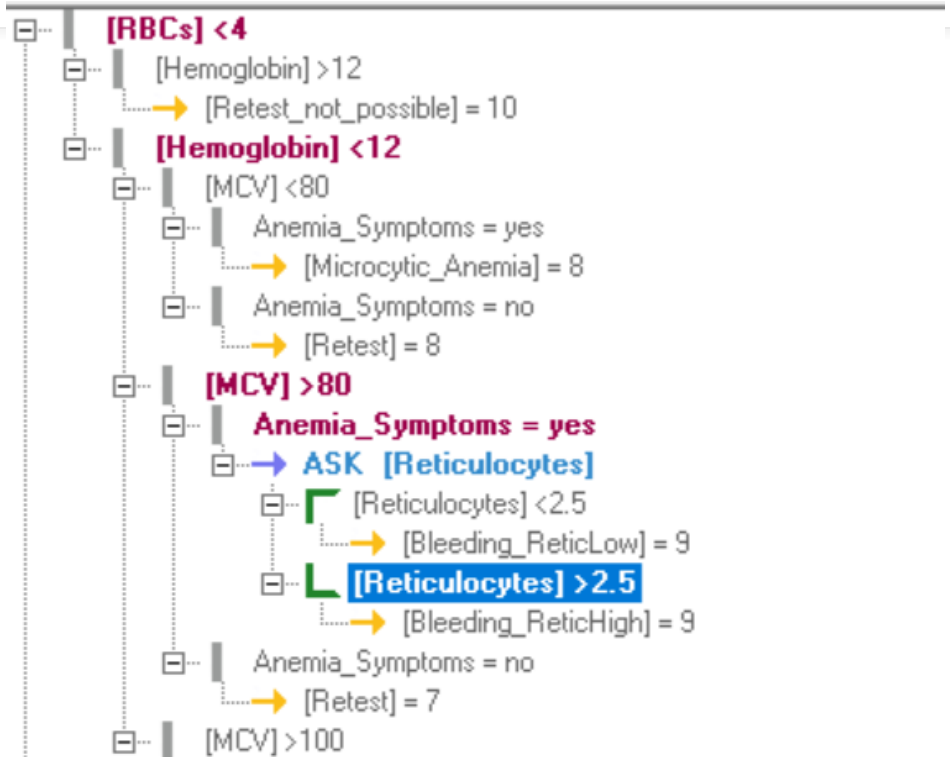


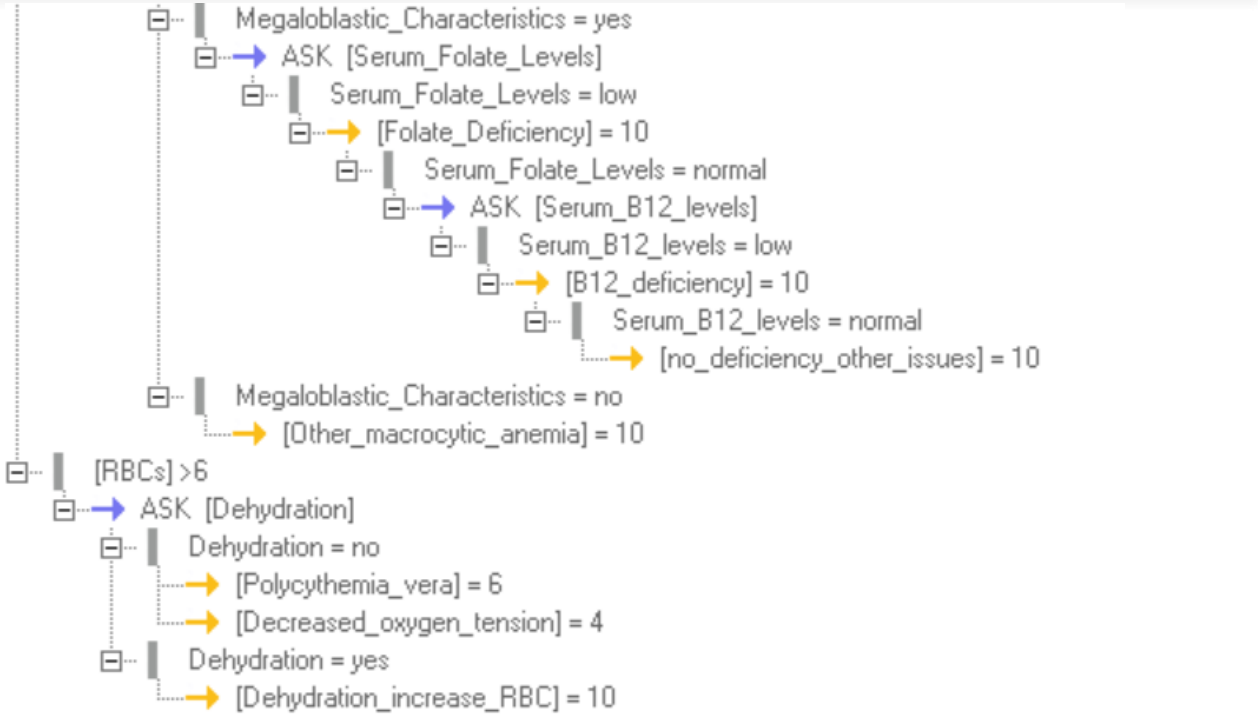
If RBCs, WBCs, PLTs, Hemoglobin, Hematocrit, and Reticulocytes are all normal, the patient is most likely healthy. The first logic block expresses this, giving the physician a “no further testing required” result.

Corvid Process: Red Blood Cell Disorders

- If my red blood cells were at an abnormal amount, my CORVID process would automatically start my “red blood cell abnormality logic block (see on subsequent slide).”
- An increase in red blood cells would ask the physician if the patient has the disorder polycythemia vera or is simply dehydrated
- A decrease in red blood cells would go through all the anemias and assess bleeding using hemoglobin and MCV values. Anemias are divided into macrocytic, microcytic, and normocytic anemias (size of the white blood cells), which is given by the MCV values.
- There are also places where the physician would have to retest. For example, it is impossible for red blood cell values to be low and for hemoglobin values to be normal. In this case, a patient must be retested.
- Examples will be provided on later slides

Red Blood Cell Abnormalities Logic Block:

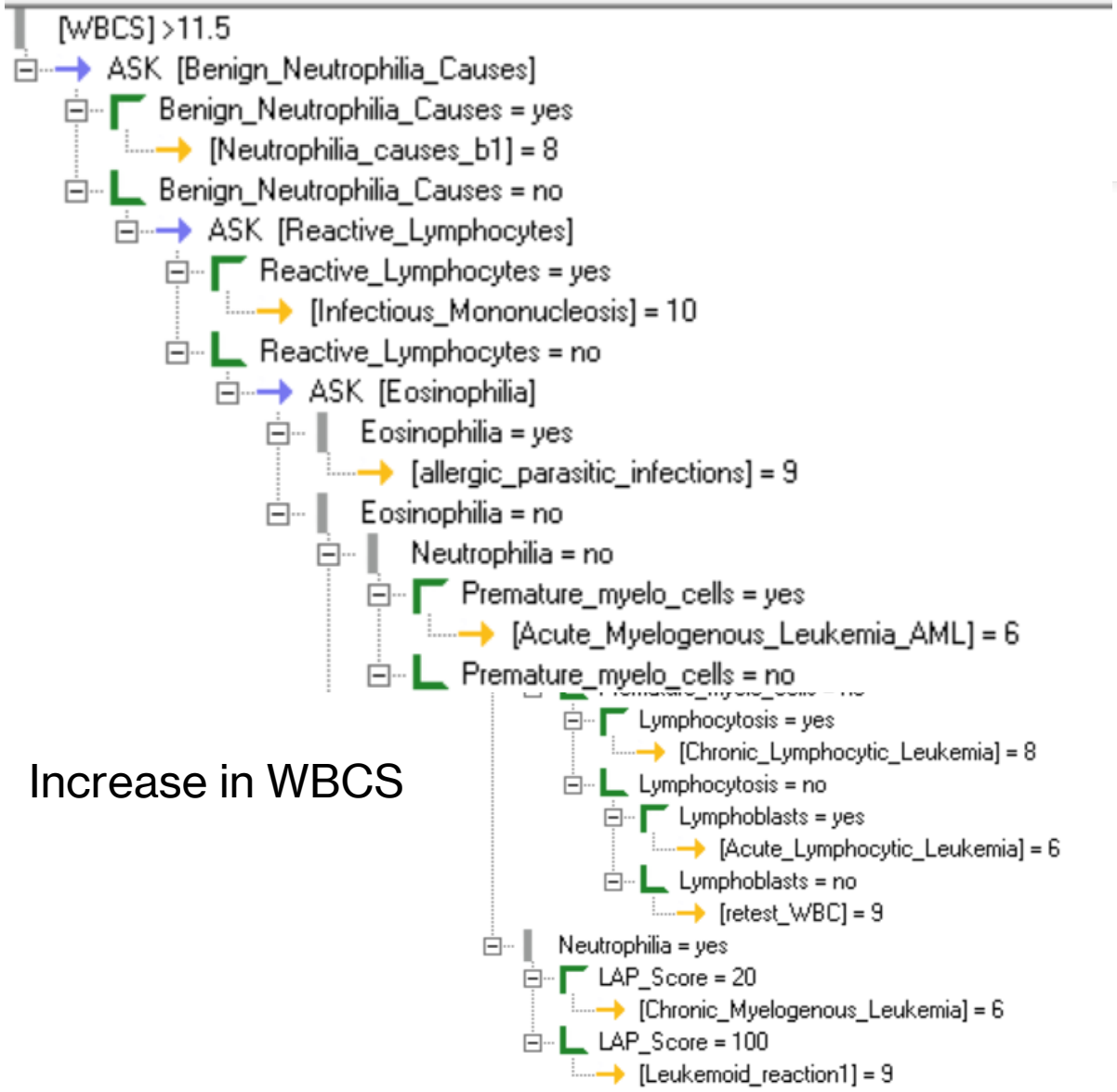




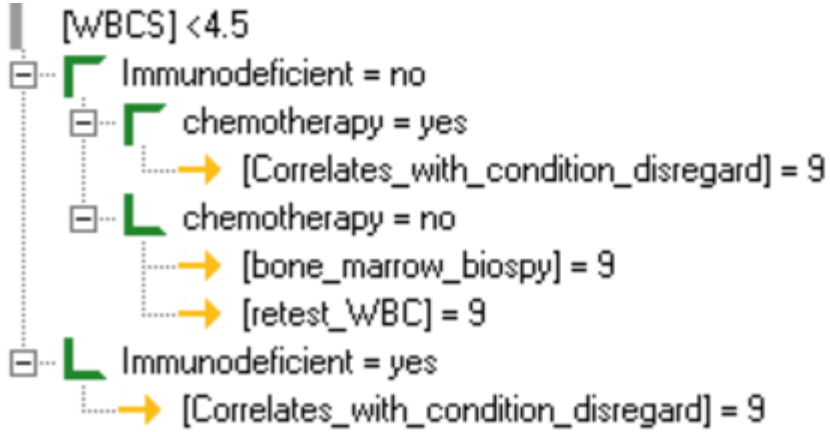
Corvid Process: White Blood Cell Disorders

- If my white blood cells had an abnormal count value, the CORVID process would automatically start the “White Blood Cell Abnormalities” logic block (see on next slide).
- An increase in WBCs would cause this logic block to rule out infections, allergic reactions, and stress responses before finally heading towards a leukemia route.
- A decrease in WBCs would rule out immunosuppression through disease and radiation before heading towards bone marrow failure.
- In cases of leukemias and bone marrow failure, the physician would be asked to perform a bone marrow biopsy. This is where our system ends, as the bone marrow biopsy has its own plethora of rules, molecular tests, and values that would confirm the diagnosis.
- If a disease could not be provided, the doctor will be asked to retest and to perform a bone marrow biopsy if appropriate.
- Examples will be provided in subsequent slides.

White Blood Cell Abnormalities Logic Block:



Increase in WBCS



Decrease in white blood cells

Red Blood Cell Case Study #1

- A pregnant woman comes into the physician office looking pale and complains of excessive fatigue. She told the doctor she has not been taking prenatal vitamins. The doctor orders a CBC, where he sees low red blood cell, white blood cell, platelet, and hemoglobin levels, with a high red blood cell MCV. The technologist reported that her peripheral blood smear showed hyper-segmented neutrophils, oval large red blood cells, and pancytopenia (meaning red blood cells, white blood cells, and platelets are low) He also orders a vitamin panel since she mentioned not taking her prenatal vitamins and sees her folate levels are low.
- The doctor decides to use the CDSS to figure out the patient's diagnosis.

LAB RESULTS:
RBCS: 2.5 Low
HGB: 9 Low
MCH: 20 Low
MCHC:23 Low
MCV: 130 High
WBCS: 3.0 Low
PLTS: 80 Low
FOLATE: Low

Red Blood Cell Case #1

Exsys Servlet Runtime

What is the hemoglobin level? 9.0

What is the absolute red blood cell count? 2.5

What is the mean cell volume? (MCV) 130.0

What is the absolute white blood cell count? 3.0

Does the blood smear show megaloblastic characteristics in red blood cells, such as hypersegmented neutrophils, oval macrocytes, and pancytopenia? yes

Order serum folate and B12 tests. What is the serum folate level of the patient? low

The patient has macrocytic anemia caused by folate deficiency. This can be caused by inadequate intake, increased requirements, impaired absorption, antifolate drugs, and excessive loss (renal dialysis). Please figure out the source of the folate deficiency and treat accordingly. Conf=10.0

Please retest the patient for their abnormal white blood cell result as we are unable to hone in on a disease. Please take a bone marrow biopsy if deemed necesscary in case of a bone marrow failure or leukemia. Conf=8.0

Does the patient have an immunodeficiency such as HIV or are they on immunospressants? no

Is the patient currently undergoing chemotherapy or radiation therapy? no

Please take a bone marrow biopsy on this patient to rule out bone marrow failure due to low white blood cell count. Conf=8.0

Our CORVID system diagnosed the patient with macrocytic anemia caused by folate deficiency. This type of deficiency would be exaggerated in a pregnant patient, as the baby would also be using the folate in the patient's body. Our system prompts us to also retest for WBC's since they are low for an unknown reason but since we know that folate deficiency causes pancytopenia (decrease in all blood cell types, it is not necessary to retest for white blood cells.

Red Blood Cell Case #2

- A patient comes in with extreme fatigue, loss of appetite, and complains of insomnia. They have recently lost their job and gone through a divorce, and complain that it is hard to even leave bed sometimes. The doctor orders a CBC for the patient.
- The doctor suspects a blood disorder due to excessive fatigue and rapid weight loss and uses the CORVID system to determine a diagnosis

LAB RESULTS:
RBCS: 5
WBCS: 10
PLTS: 250
HGB: 16
HCT: 45
Retics: 1.3

Red Blood Cell Case Study #2

What is the hemoglobin level? 16.0

What is the hematocrit? 45.0

What is the absolute red blood cell count? 5.0

What is the absolute platelet count? 250.0

What is the absolute white blood cell count? 10.0

What is the average number of reticulocytes? 1.3

The patient has blood indices in reference range. No further testing is required. Conf=10.0

OK

The patient is overall physically healthy and shows no indication on their CBC of a blood disorder. The patient may have depression due to excessive fatigue, rapid weight loss, and is dealing with many hardships in life such as the job loss and divorce. Blood disorders, however, are ruled out.

Red Blood Cell Case Study #3

- A 50-year old male patient comes in the emergency room after a car crash and had symptoms extreme dizziness, fatigue, and vertigo. Visible bleeding in the abdomen was observed. A CBC was ordered on the patient.

LAB RESULTS:
RBCS: 1.5 LOW
WBCS: 11.5
PLTS: 151
HGB: 8 LOW
MCV: 85
MCH: 23
MCHC:25
RETICS: 5.0% HIGH

Red Blood Cell Case Study #3

What is the hemoglobin level? 8.0

What is the absolute red blood cell count? 1.5

What is the mean cell volume? (MCV) 85.0

What is the absolute white blood cell count? 11.5

What is the average number of reticulocytes? 5.0

Does the patient have symptoms of fatigue, pallor, vertigo, or dyspnea? yes

Possible blood loss that is being made up by increase of reticulocytes. Please check for bleeding. If there is no bleeding, get a bone marrow biopsy for possible destruction of bone marrow
Conf=9.0

OK

The system detected that the patient had bleeding and that the body was responding to the bleed. The
physician can still order blood transfusion if the bleeding is excessive. Had the number of premature red blood cells not been high to accommodate for the bleeding, the physician can address the possible bone marrow failure and done an additional bone marrow biopsy once the patient's original symptoms from the car crash were taken care of.

White Blood Cell Case Study #1

- A patient comes in the ER with fever, fatigue, shortness of breath, rapid heart rate, and shivering. The doctor orders a CBC as well as blood cultures. The CBC had an increased level of white blood cells, so the doctor also ordered a leukocyte alkaline phosphatase (LAP) test as well as a manual cell differentiation count.
- The doctor wasn't sure if the patient was undergoing sepsis or other complications, so the CORVID CDSS was used to determine the patient diagnosis.

LAB RESULTS:
RBCS: 5
MCV:80
MCH: 27
PLTS: 300
MCHC: 33
WBCS: 16 HIGH
CELL DIFF: Neutrophils 90% HIGH
Eosinophils 1%
Lymphocytes: 8% LOW
Basophils: 1%
HGB: 16
HCT:46

LAP SCORE=105
Blood Cultures: Pending (can take up To five days to grow)

White Blood Cell Case Study #1

What is the absolute red blood cell count? 5.0

What is the absolute white blood cell count? 16.0

Does the patient have high levels of stress, on cortisone therapy, or partakes in strenuous exercise? no

The patient has an exaggerated leukemoid reaction to intense infection, toxic state, hemorrhage, hemoylsis, or inflammation. Please order blood cultures, toxicity panels, look for signs of bleeding, and look for signs of inflammation. Conf=10.0

Does the blood smear show an increase number of reactive lymphocytes? no

Does the patient have an abnormal increase in eosinophils? no

Does the patient have an increased number of neutrophils in their peripheral blood smear? yes

What is the patient's LAP (Leukocytic Alkaline Phosphatase) score? (extent to which the white blood cells produce leukocyte phosphtase in an infection). greater than 100

OK

The physician now has reason to believe in infection for the patient, perhaps even sepsis due to the rapid heart rate. The physician should treat the patient accordingly for the symptoms of a possible septic infection, and wait on the blood cultures to become positive so he can treat the patient with the appropriate antibiotics.

White Blood Cell Case Study #2

- A 65 year old female patient visits her primary physician. She tells the doctor she's been getting sick more than usual lately, and has been losing an excessive amount of weight. She also wakes up in night sweats and noticed swelling in her stomach.
- The doctor orders a CBC with a manual differential cell count to be done to rule out infections or a possible leukemia.

LAB RESULTS:
RBCS: 5.7
MCV:90
MCH: 30
MCHC: 35
PLTS: 190
WBCS: 17 HIGH
CELL DIFF: Neutrophils 30%
Eosinophils: 2
Lymphocytes: 68%
Basophils: 0%
HGB: 16
HCT:46

White Blood Cell Case Study #2

What is the absolute red blood cell count? 5.7

What is the absolute white blood cell count? 17.0

Does the patient have high levels of stress, on cortisone therapy, or partakes in strenuous exercise? no

Does the blood smear show an increase number of reactive lymphocytes? no

Does the patient have an abnormal increase in eosinophils? no

Does the patient have an increased number of neutrophils in their peripheral blood smear? no

Does the patient have premature white blood cells in their peripheral blood smear, such as Myeloblasts? no

Does the patient have a largely increased number of lymphocytes in their peripheral blood smear? yes

The patient is suspected to have chronic lymphocytic leukemia, especially if they are over the age of 65. Please take a bone marrow biopsy to confirm the diagnosis. Conf=7.0

OK

The patient is suspected to have chronic leukocytic leukemia, as indicated by her peripheral blood smear, symptoms, and age. The CORVID system had to rule out other possibilities of infection and leukemias to get to the final conclusion. The physician must now confirm the diagnosis with a bone marrow biopsy to run molecular tests on. The increase of lymphocytes in this disease are not immunocompetent, which explains the increased infections.

White Blood Cell Case Study #3

- A 16 year old male comes in complaining of extreme fatigue, enlarged lymph nodes, sore throat, and hepatomegaly (enlarged liver).
- The doctor orders a CBC with a manual differential for the patient, as well as a liver enzyme panel for the enlarged liver.

LAB RESULTS:
RBCS: 4.9
MCV:95
MCH: 31
MCHC: 35
PLTS: 320
WBCS: 13 HIGH
CELL DIFF: Neutrophils 40%
Eosinophils: 4%
Lymphocytes: 56%
*Note: 32% Reactive Lymphocytes, 24% regular lymphocytes
Basophils: 0%
HGB: 16
HCT:46
Liver Enzymes: HIGH

White Blood Cell Case Study #3

What is the absolute red blood cell count? 4.9

What is the absolute white blood cell count? 13.0

Does the patient have high levels of stress, on cortisone therapy, or partakes in strenuous exercise? no

Does the blood smear show an increase number of reactive lymphocytes? yes

The patient may have infectious mononucleosis, resulting in an increased production of reactive lymphocytes. Please perform molecular tests to detect the Epstein-Barr Virus Conf=10.0

OK

- Because reactive lymphocytes are so closely related to the manifestation of the disease Infectious mononucleosis, the system automatically correlates the two. The patient's age and elevated liver enzymes also indicate Infectious mononucleosis. Molecular tests to confirm the Epstein-Barr Virus which causes the disease will confirm the diagnosis.

Conclusion:

- Because of the large number of variables in lab results, physicians may find it difficult to rule out different blood disorders because of the variety of diseases as well as clinical findings that are indicative all the diseases
- Creating an expert system to allow physicians to navigate through the different lab results would save time and increase the quality of patient care
- Although this project was an oversimplified version of an expert system that a hospital would actually adopt, which would have many more logic blocks and decision tree nodes, a rule-based data-driven design similar to this COVID process can be extremely useful if incorporated with lab results in the future.

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