Making Sense of Blood Cancer Test Results

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University of Michigan Medical School | Michigan Medicine

Pacific Northwest MM Fighters | Saturday, August 22, 2026 | 10:00 a.m. Pacific

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WHY A PATHOLOGIST IS TALKING TO YOU TODAY

The doctor you never meet

We never see you

- Your oncologist sees the person
- I see what the person is made of
- Two views of the same illness

We establish ground truth

- **Every treatment decision starts with a diagnosis**
- That diagnosis is a laboratory product
- It has a maker, a method and a margin of error

We write the report

- The line in your chart that says what you have
- Regimens, trials and insurance all key off it
- You are entitled to read it

None of your numbers arrive by magic. Each one is made by a person using a method, and once you know the method you can tell a meaningful change from noise.

ROADMAP

What this hour covers

1. **The procedure**
   What is taken, and why the first pull matters
2. **The microscope**
   How a plasma cell percentage is actually counted
3. **The stains**
   Immunohistochemistry, kappa and lambda
4. **Flow cytometry**
   Lasers reading cells one at a time
5. **FISH and genetics**
   Where risk category comes from
6. **MRD and clonoSEQ**
   How one in a million is found
7. **Blood tests**
   M spike, light chains, CRAB and response
8. **The whole family**
   MGUS, plasmacytoma, amyloidosis and the rest
9. **Your report**
   How to read it, what to ask

1 The procedure and the specimen

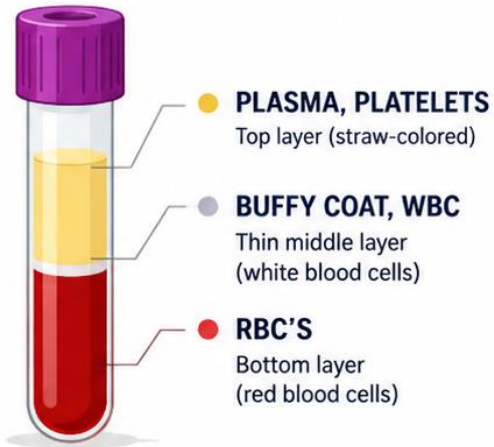
COLLECTION: VENIPUNCTURE

TUBES OF BLOOD

ANTICOAGULATED
Cells, plasma

PURPLE	GREEN	YELLOW	BLUE
EDTA	Heparin	ACD	NaCit
EDTA (K_2EDTA)	Heparin (Lithium/ Sodium)	ACD (Acid Citrate Dextrose)	NaCit (Sodium Citrate)

CELLS, PLASMA



- **PLASMA, PLATELETS**
  Top layer (straw-colored)
- **BUFFY COAT, WBC**
  Thin middle layer
  (white blood cells)
- **RBC'S**
  Bottom layer
  (red blood cells)

NOT ANICOAGULATED
Clot, serum

RED
NONE

No additive
(Clot activator)

CLOT, SERUM

- **SERUM**
  Top layer (straw-colored)
  after clotting and centrifugation
- **CLOT**
  Bottom layer
  (clotted blood)

KEY POINTS

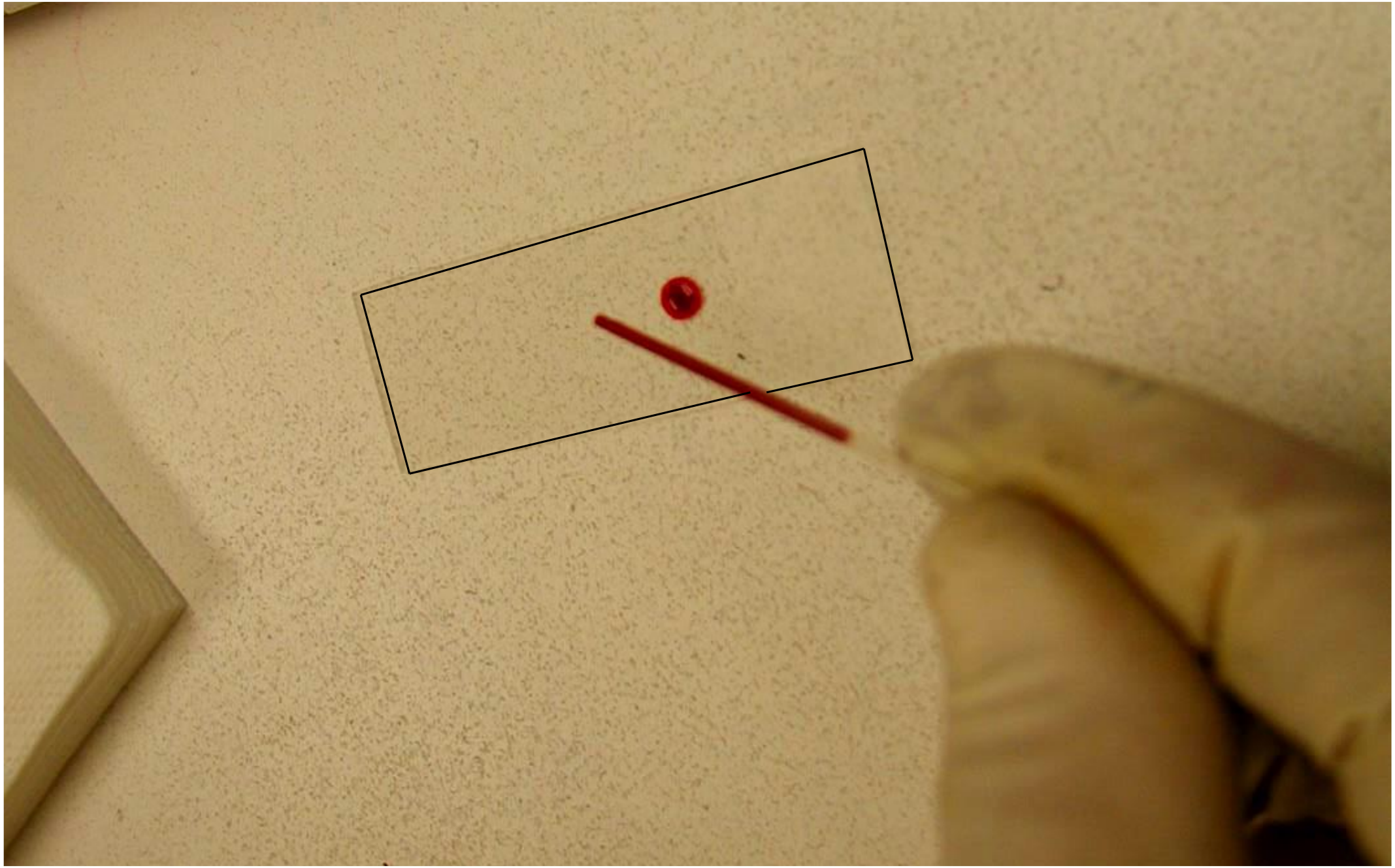
- Anticoagulated tubes prevent clotting and preserve cells for analysis.
- Non-anticoagulated tube allows clotting to obtain serum.
- Proper tube selection is essential for accurate test results.

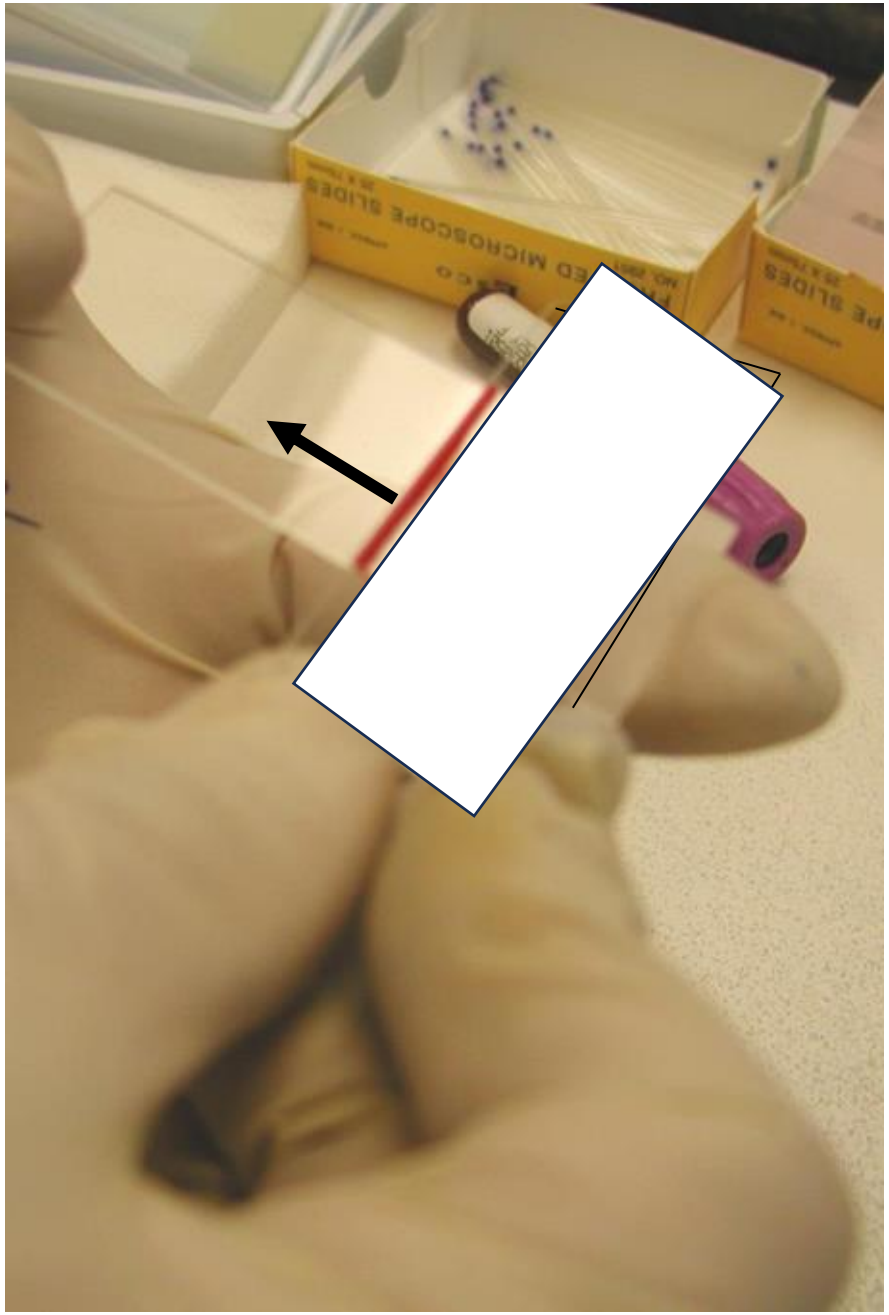
CBC:

	normal range
WBC	*3.5-11 x10^3/ul*
RBC	*4.4-5.9 x10^6/ul*
Platelet count	*150-450 x10^3/ul*
Hemoglobin	*13.5-17.5 g/dl*
Hematocrit	*41-53%*

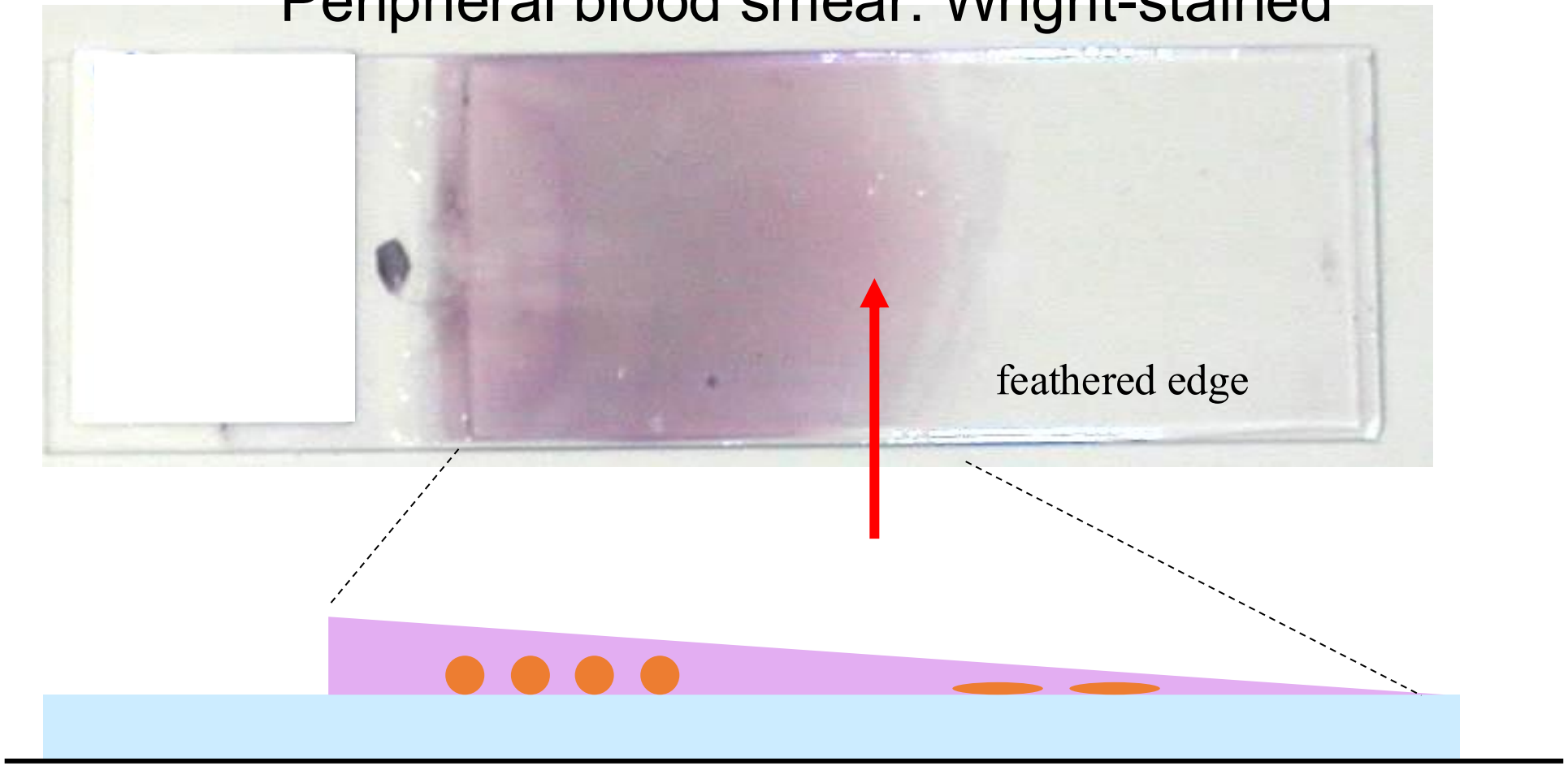
Differential count: % of types of blood cells

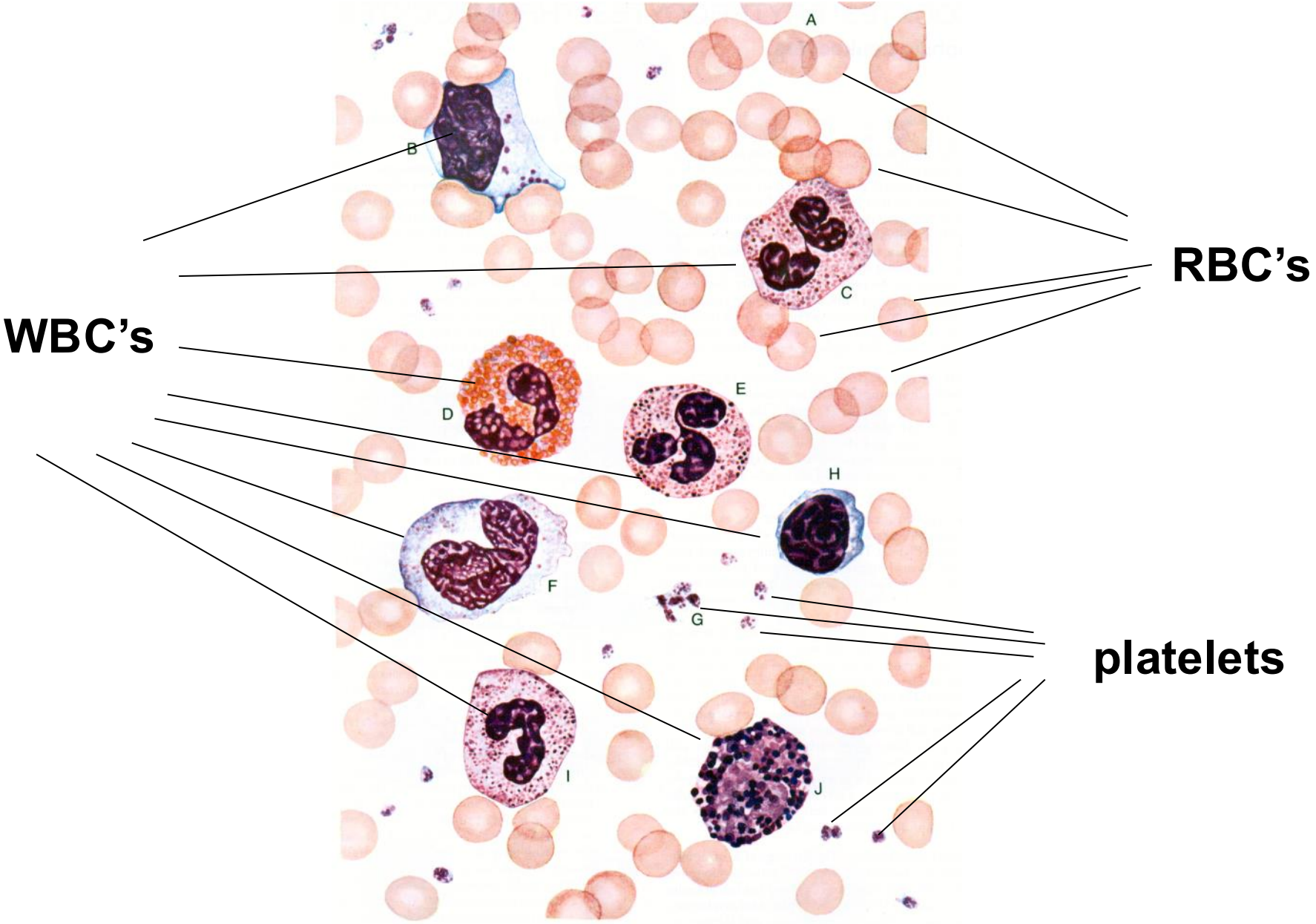
Peripheral blood smear: Wright-stained





Peripheral blood smear: Wright-stained




A
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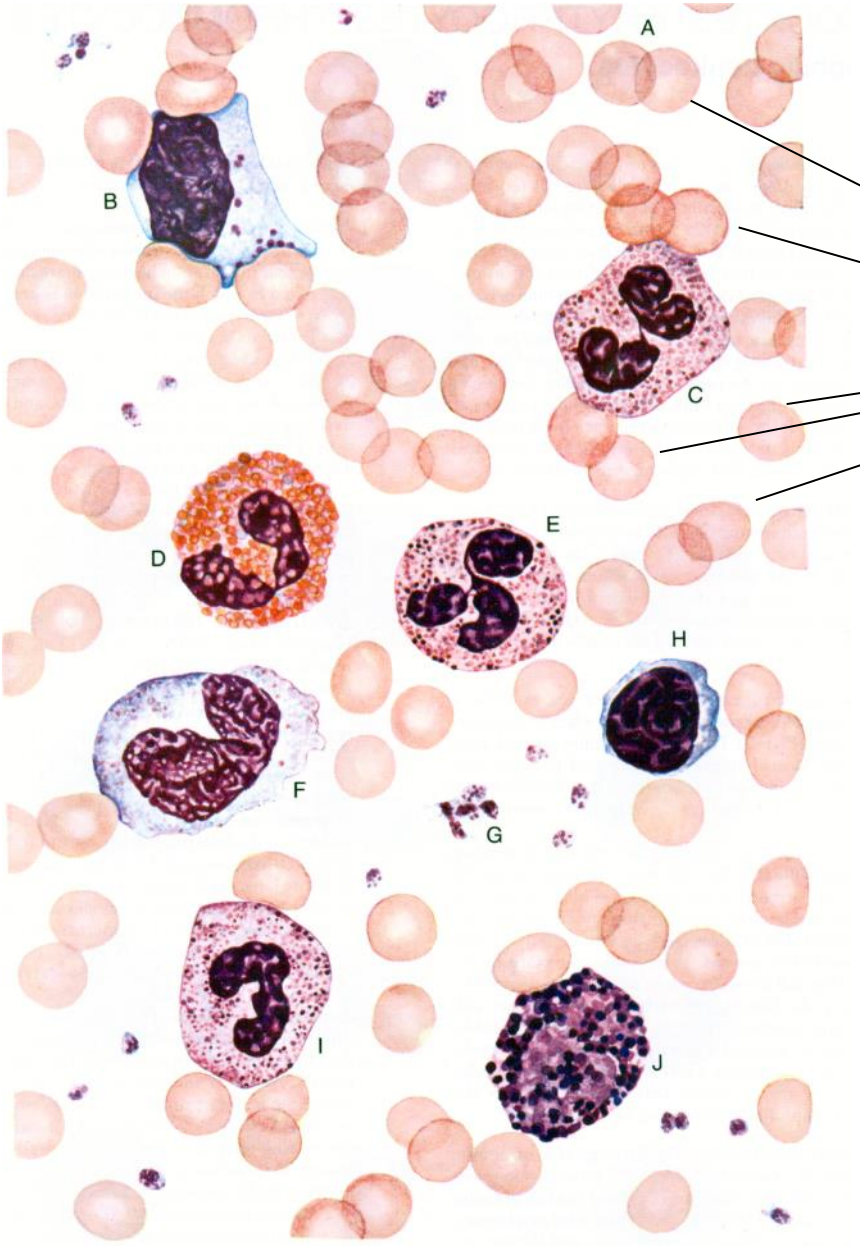
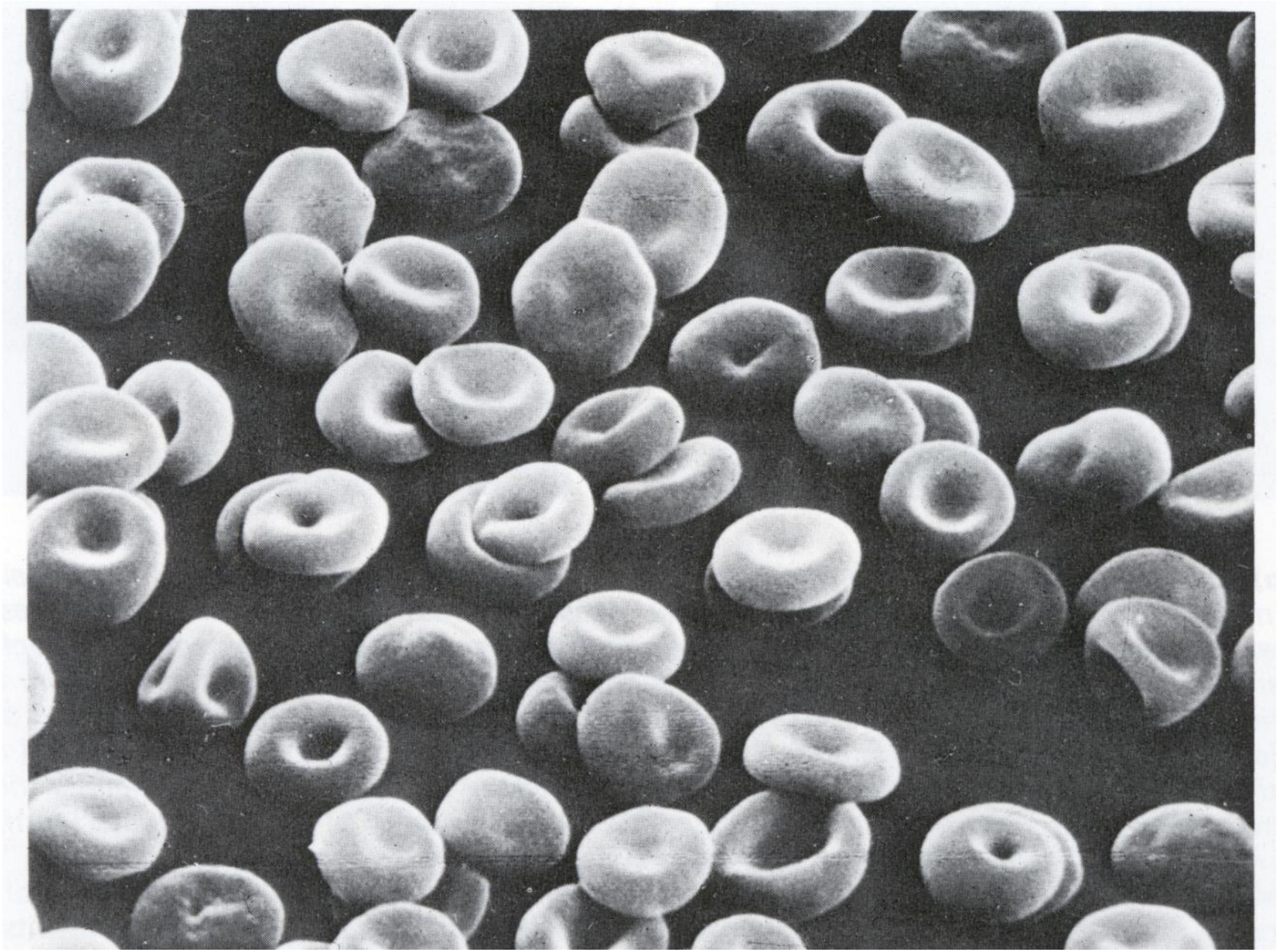
WBC's
RBC's
platelets

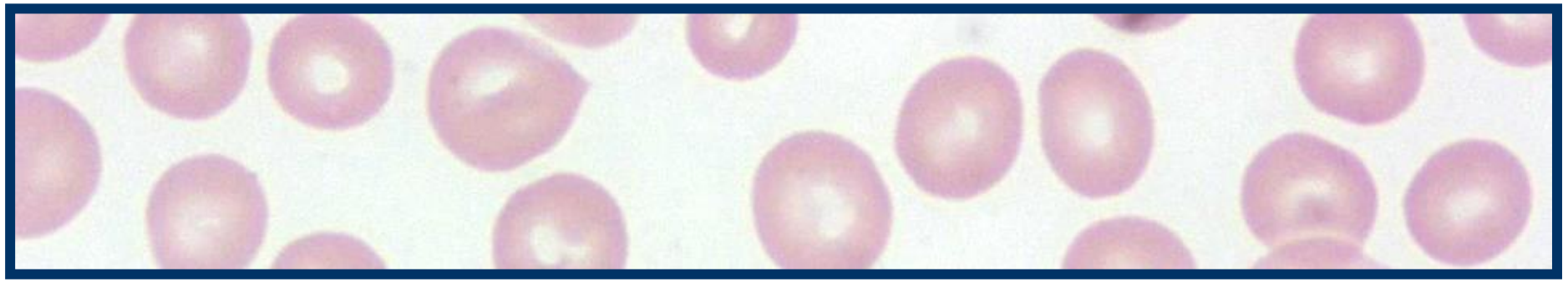


RBC's

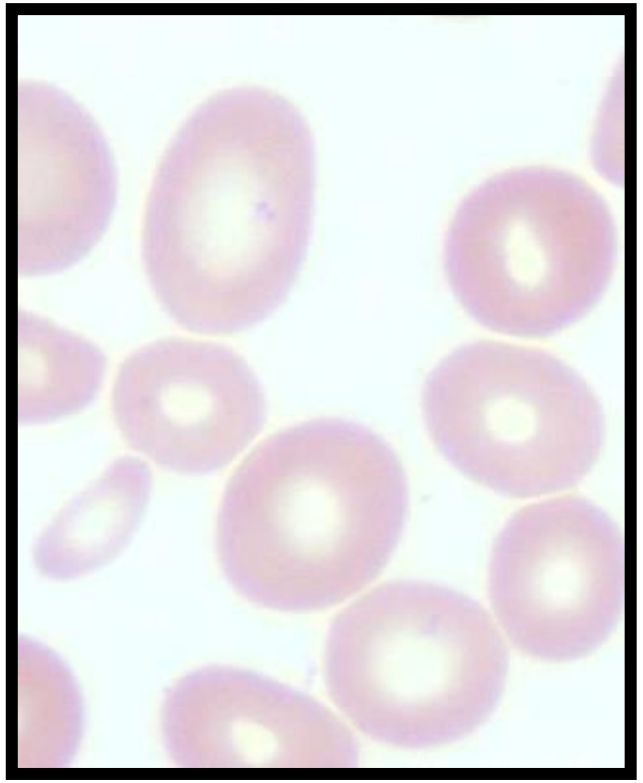
8u



Electron Microscopy

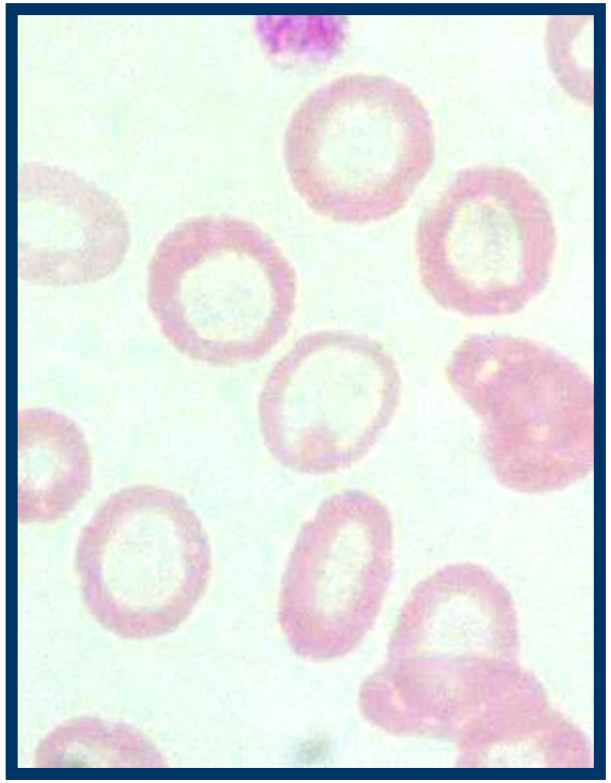


Examples of RBC Pathology



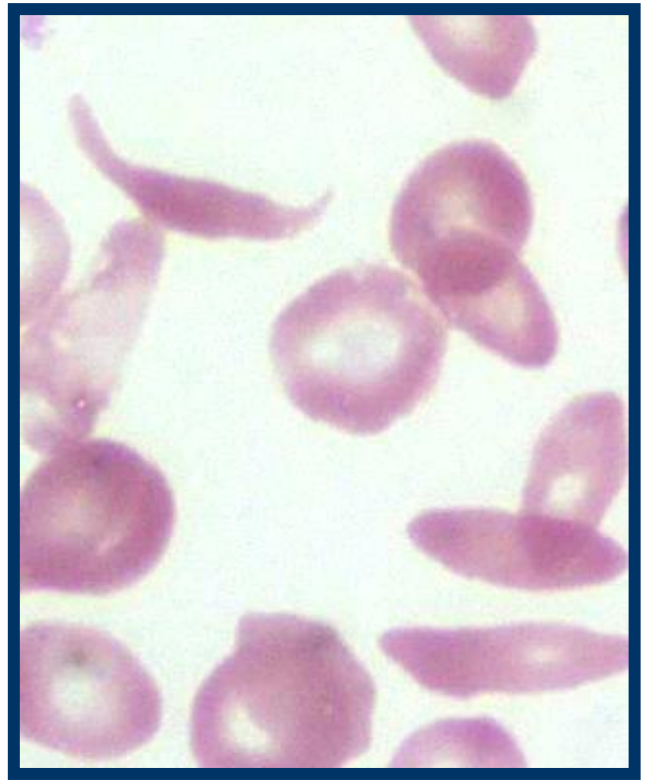
Increased size

Abnormal division



Reduced hemoglobin

Decreased Iron



RBC Sickling

Abnormal Hb (HbS)

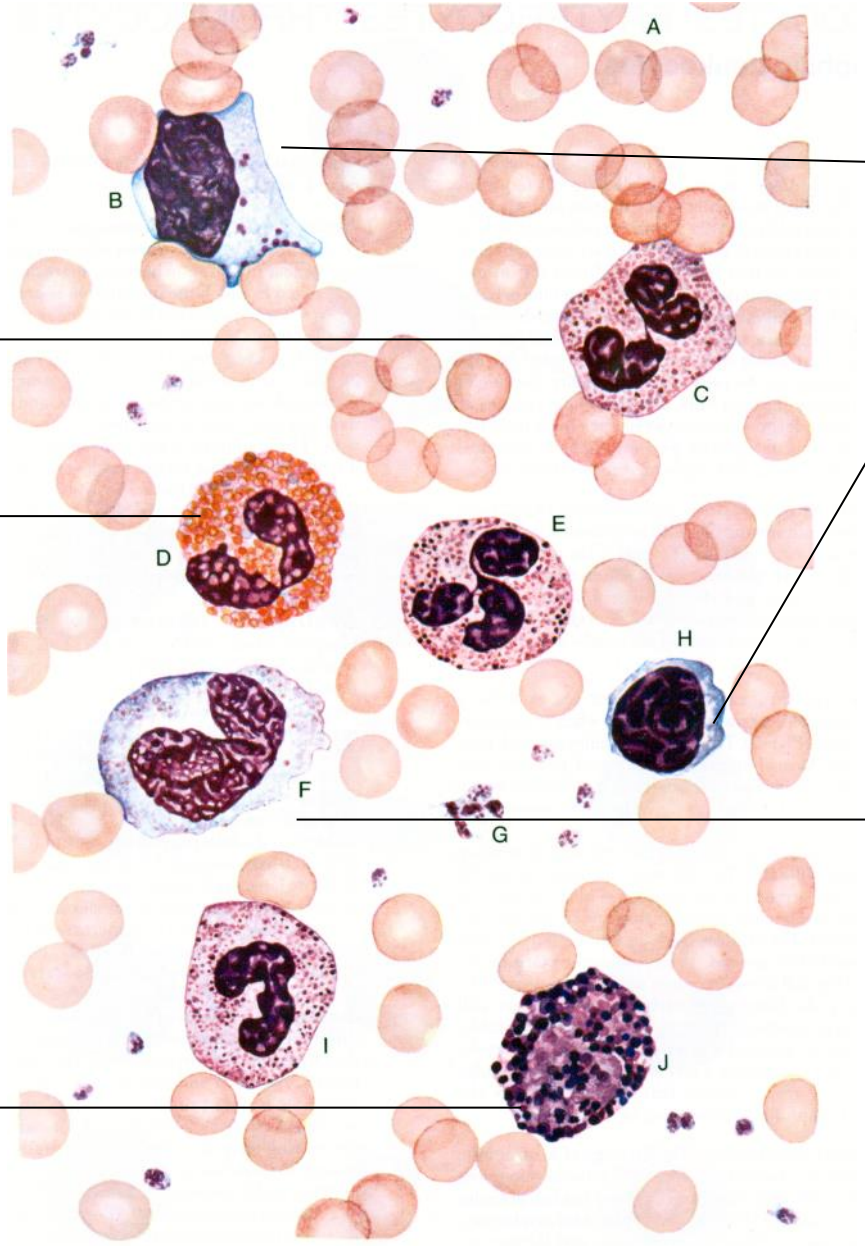
WBC's

granulocytes

-neutrophil

-eosinophil

-basophil

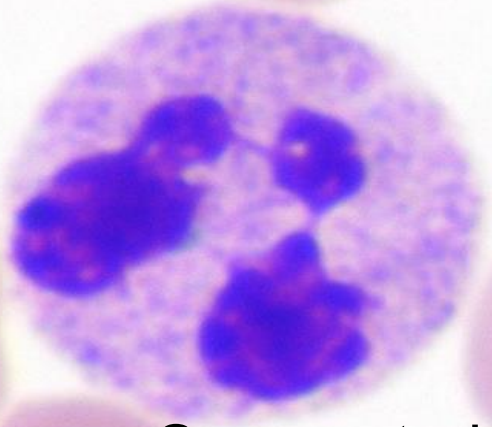


lymphocytes

monocyte

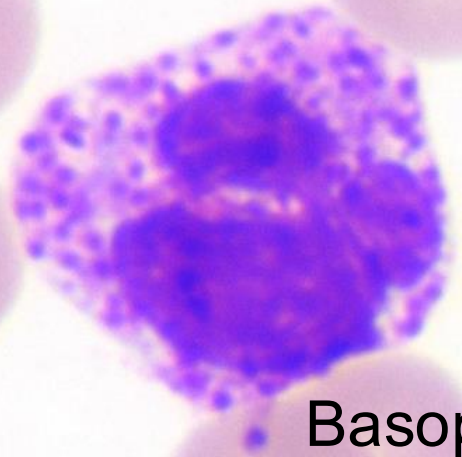
Normal Range for WBC Differential Count

Neutrophils	39-75%
Bands	0-6%
Metamyelocytes	0
Myelocytes	0
Promyelocytes	0
Blasts	0
Lymphs	16-47%
Monocytes	4-12%
Eosinophils	0-7%
Basophils	0-2%



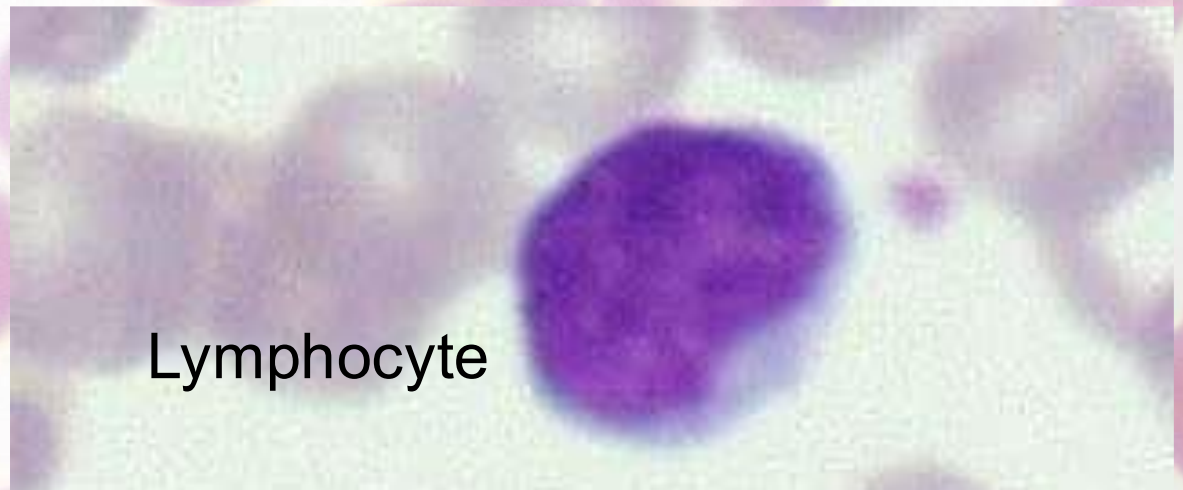
Segmented Neutrophil

"seg", "poly"

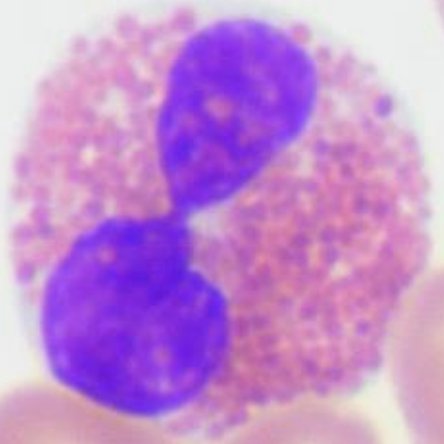


Basophil

"baso"

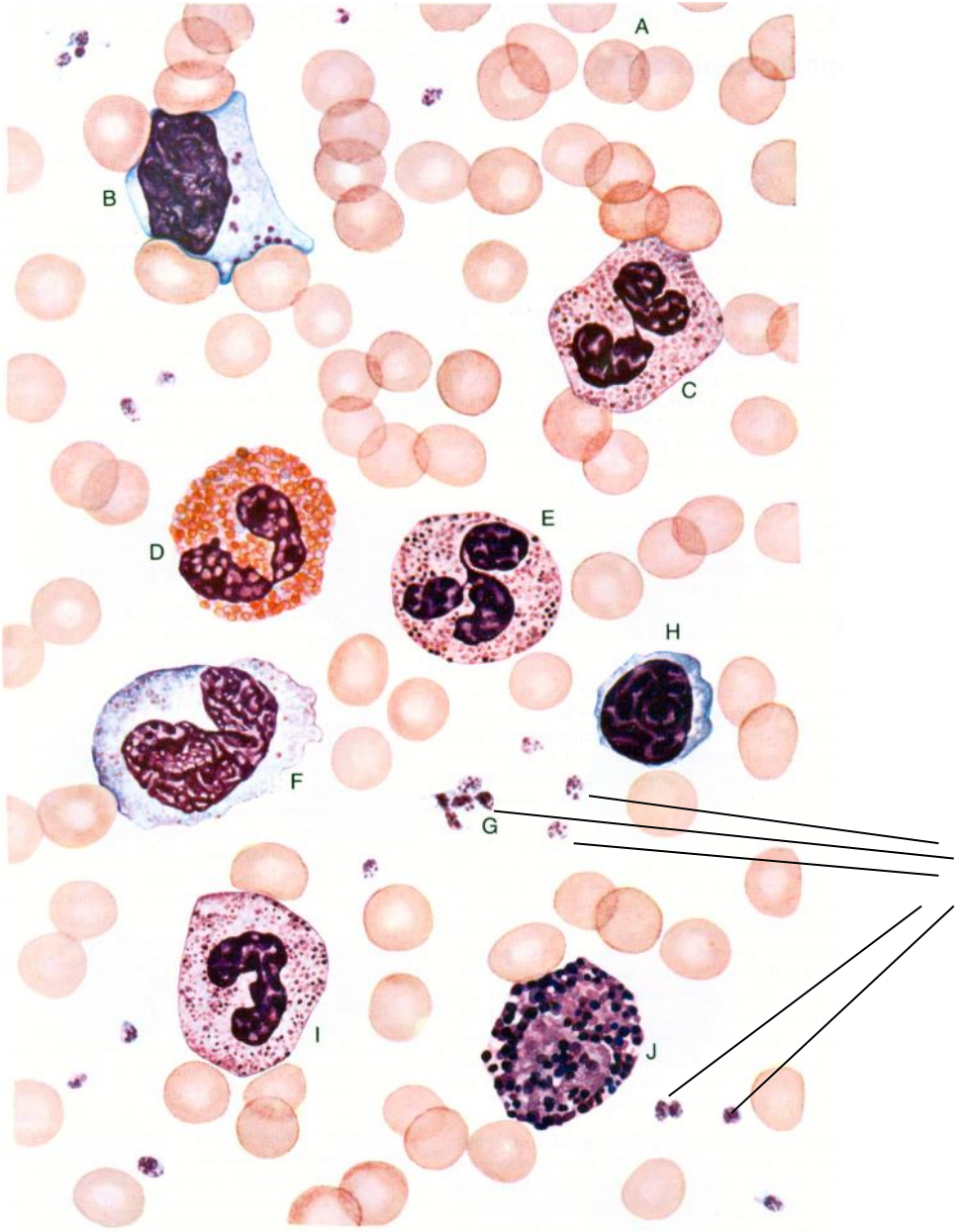


Lymphocyte



Eosinophil

"eo"


A
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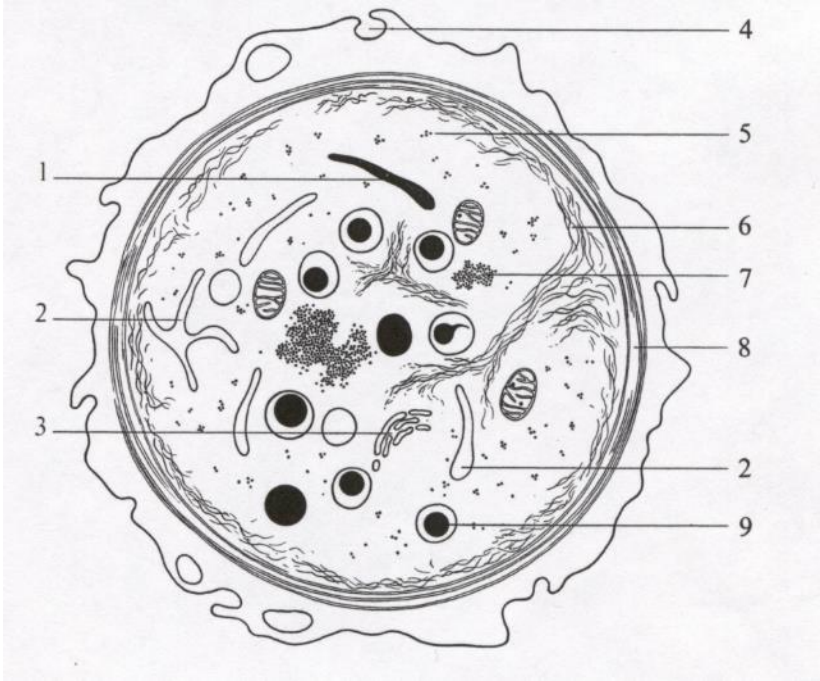
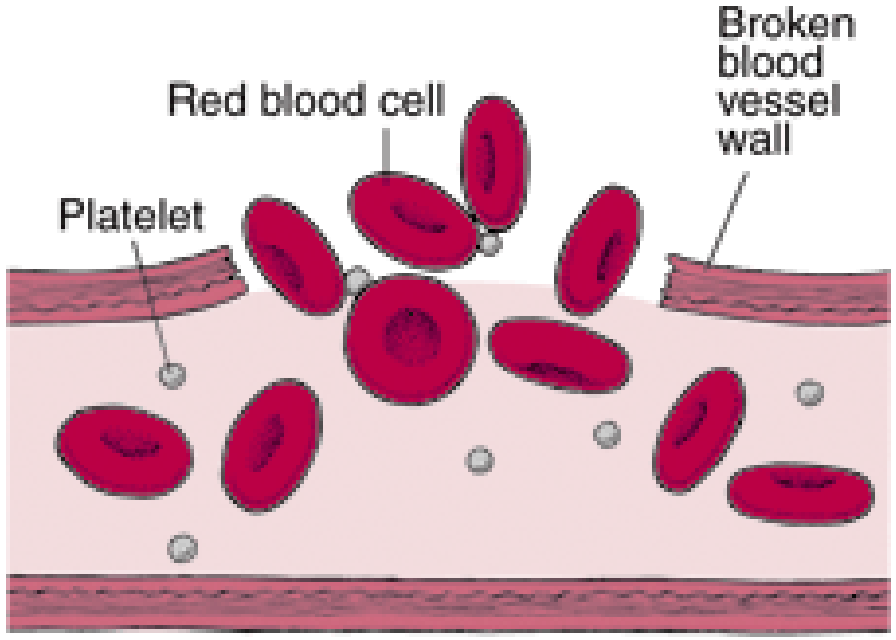
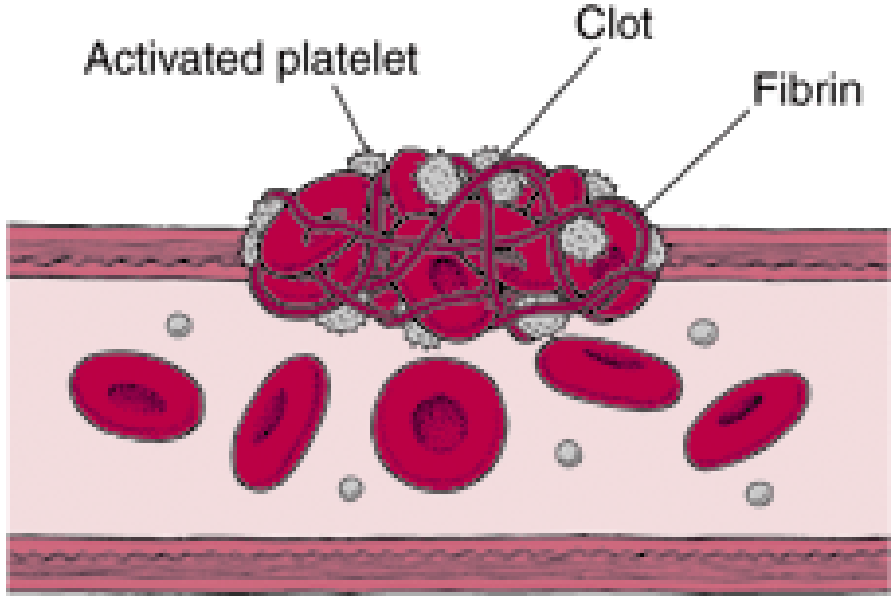
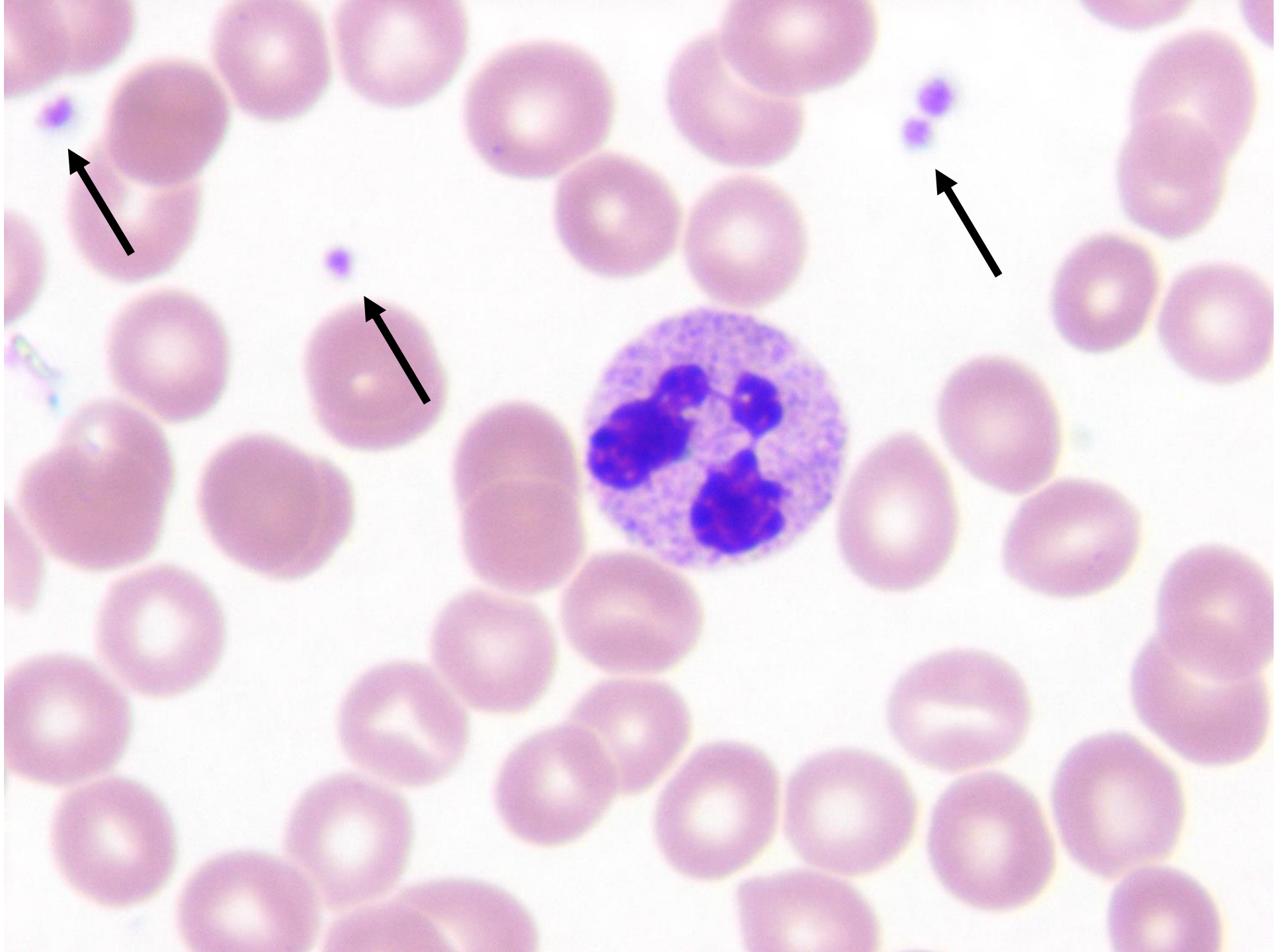
platelets


4
5
1
6
7
2
8
3
2
9

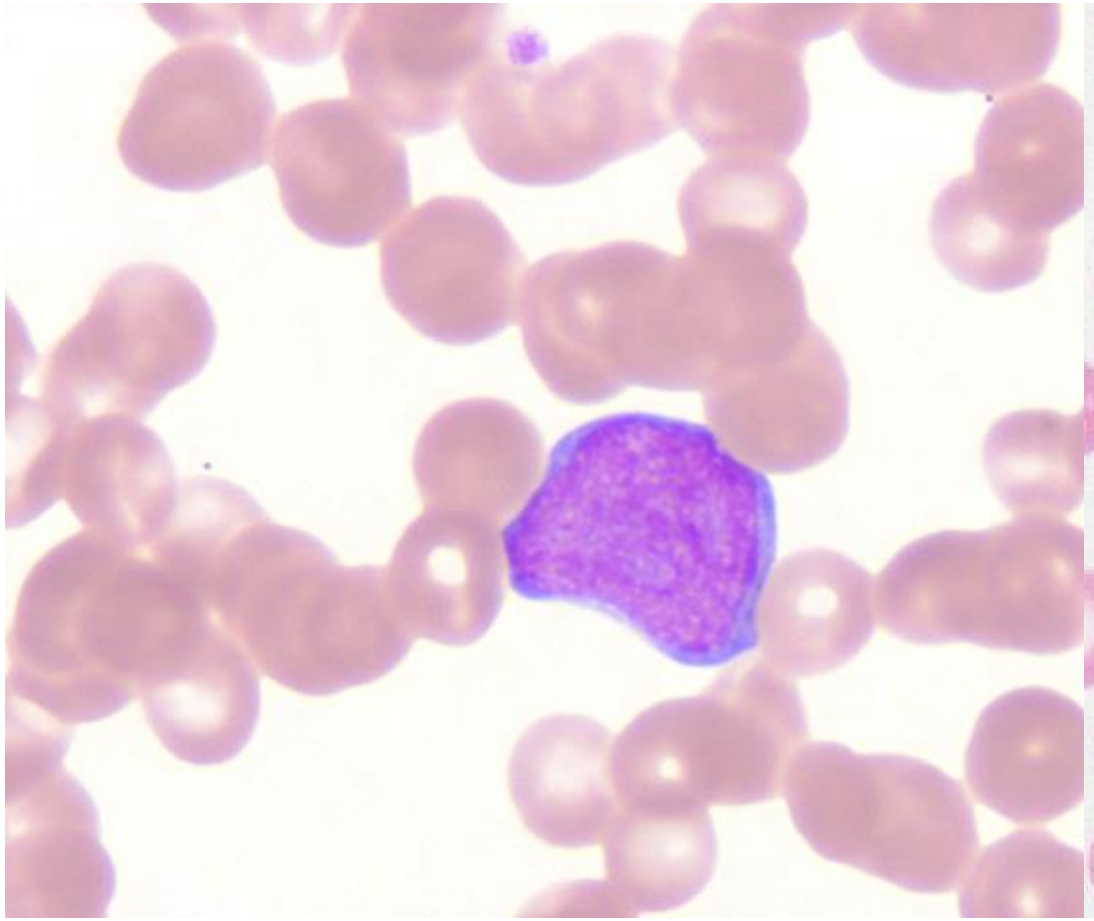
platelet

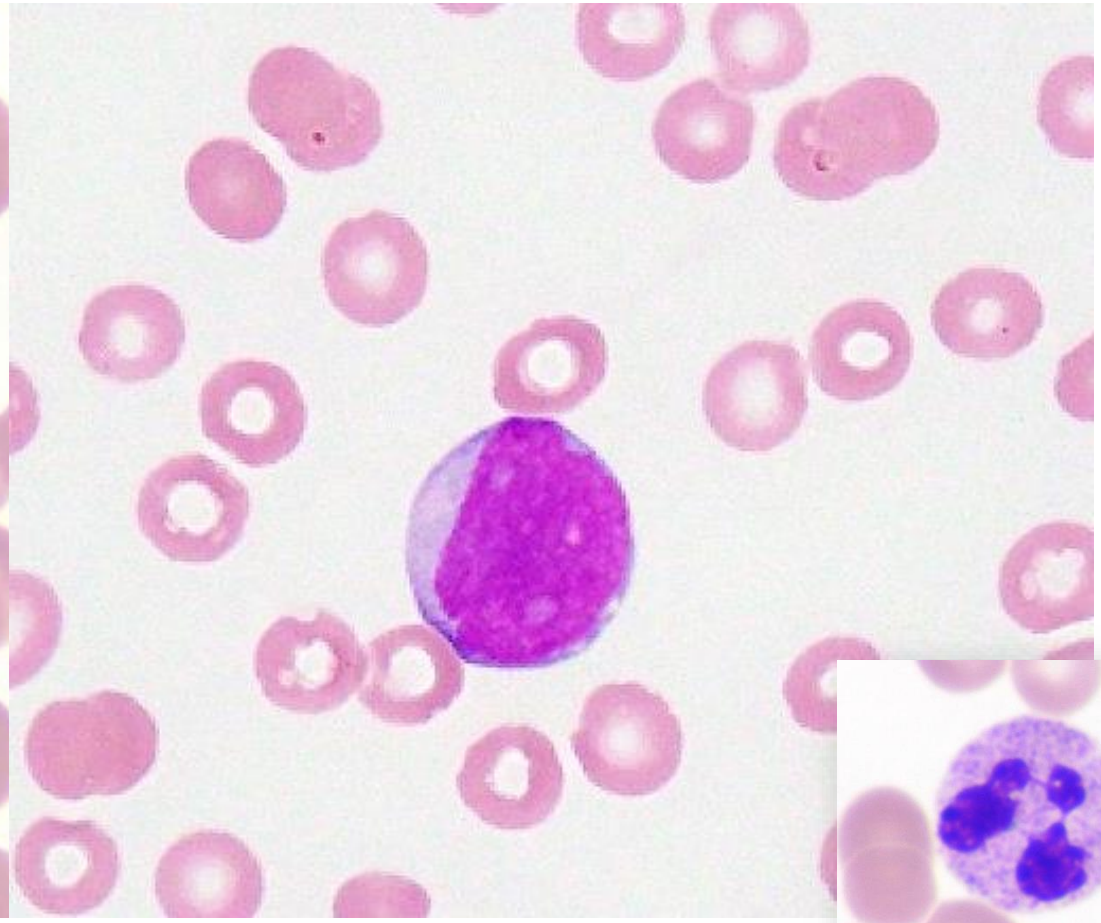

Broken blood vessel wall
Red blood cell
Platelet


Clot
Activated platelet
Fibrin

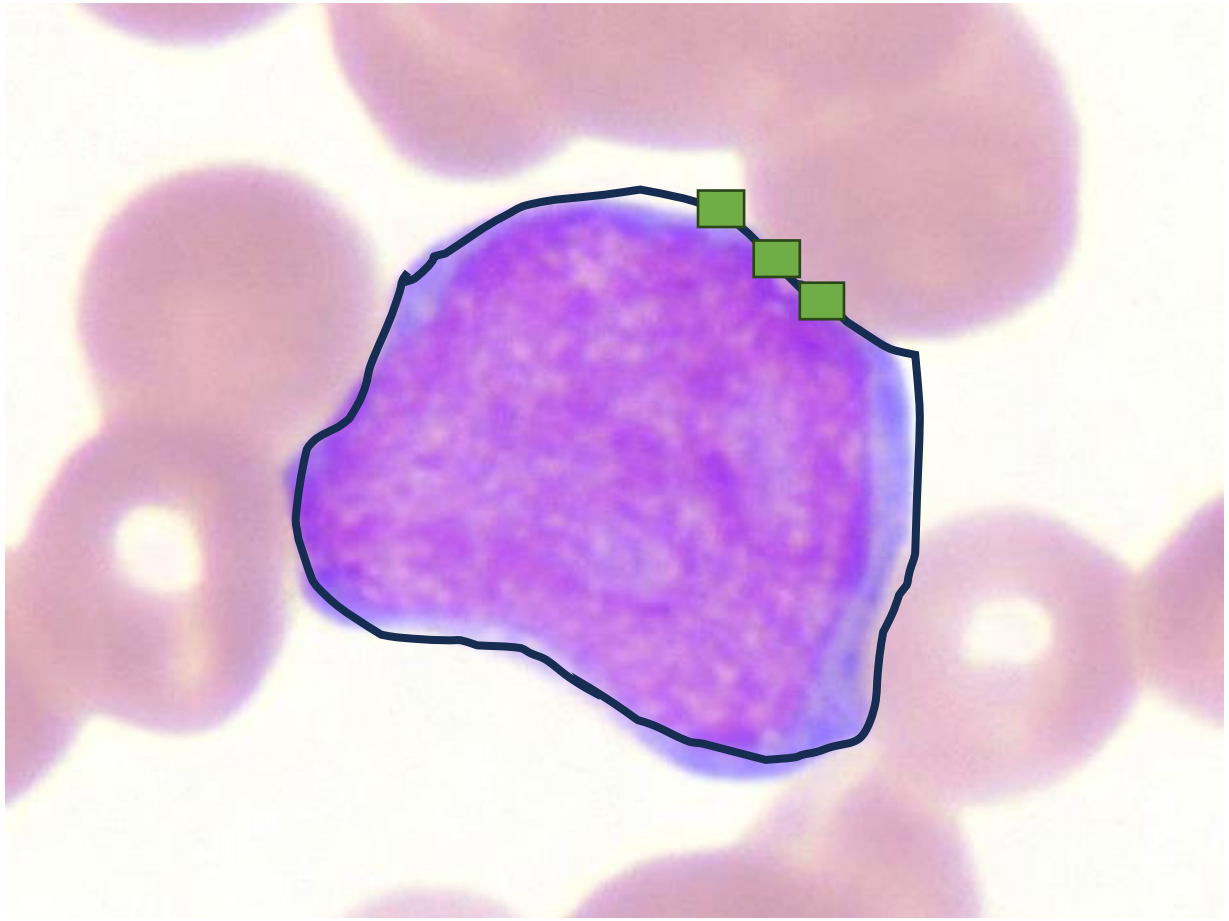


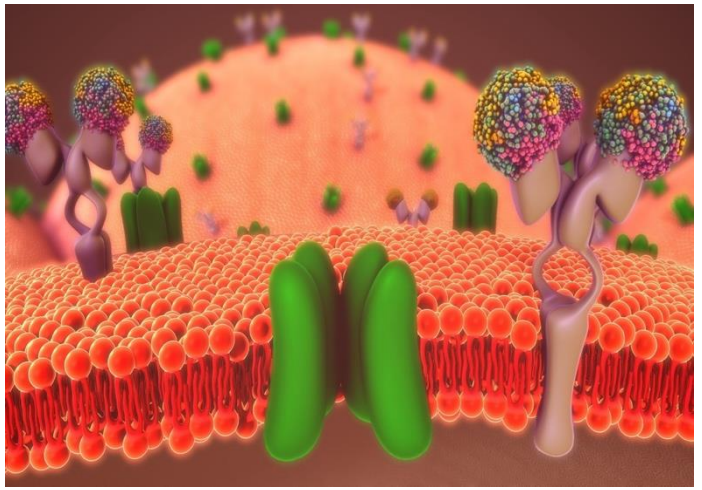
Abnormal cells

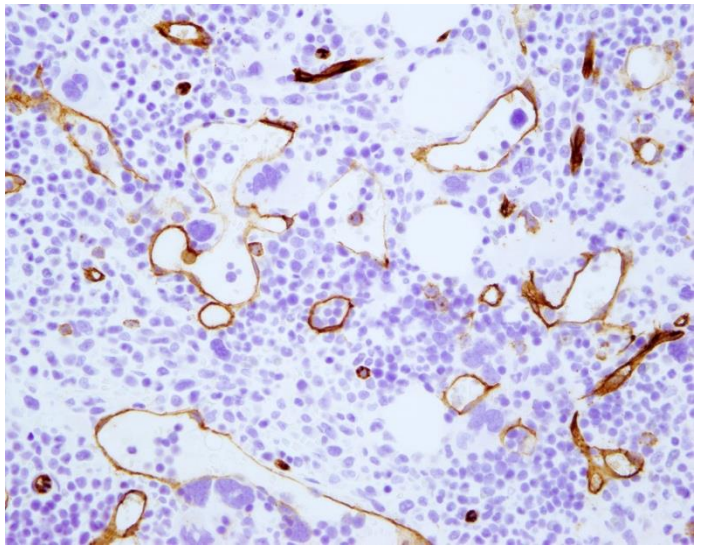




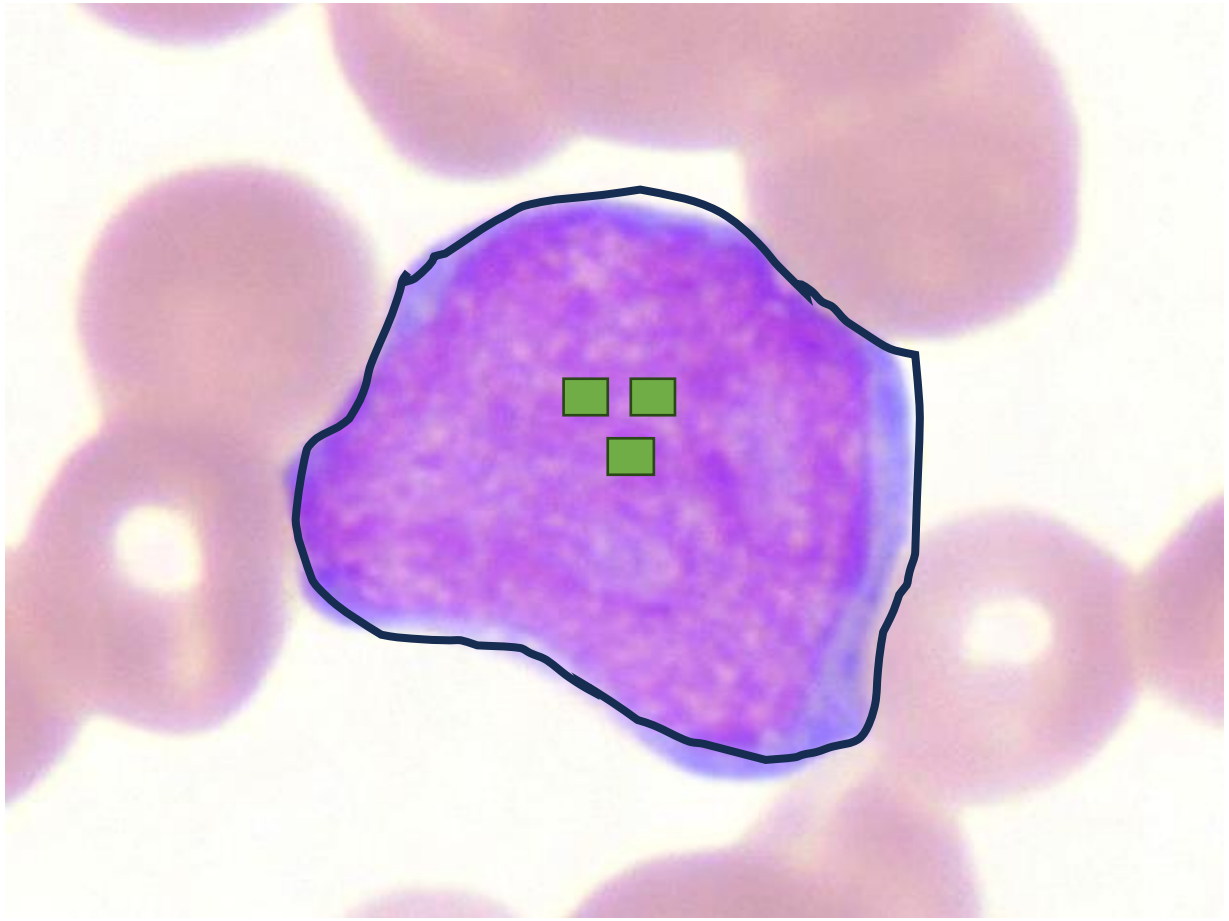
Surface markers?

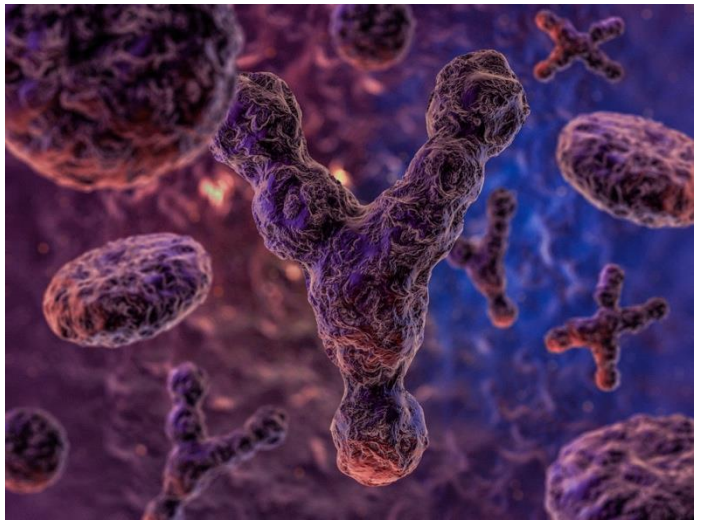


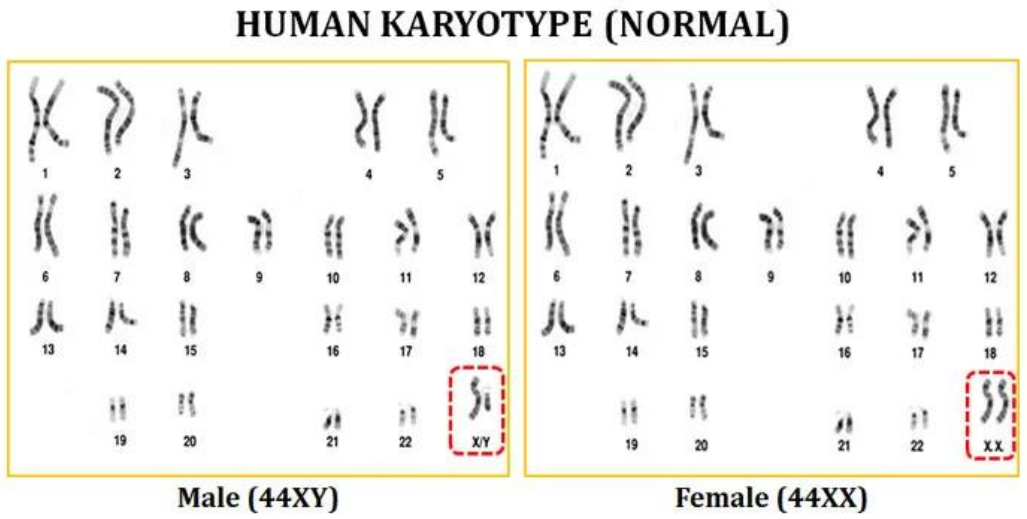




Genetics?






HUMAN KARYOTYPE (NORMAL)
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X/Y
Male (44XY)
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X X
Female (44XX)

WHERE THE ANSWER LIVES

Blood or marrow: what each one can answer

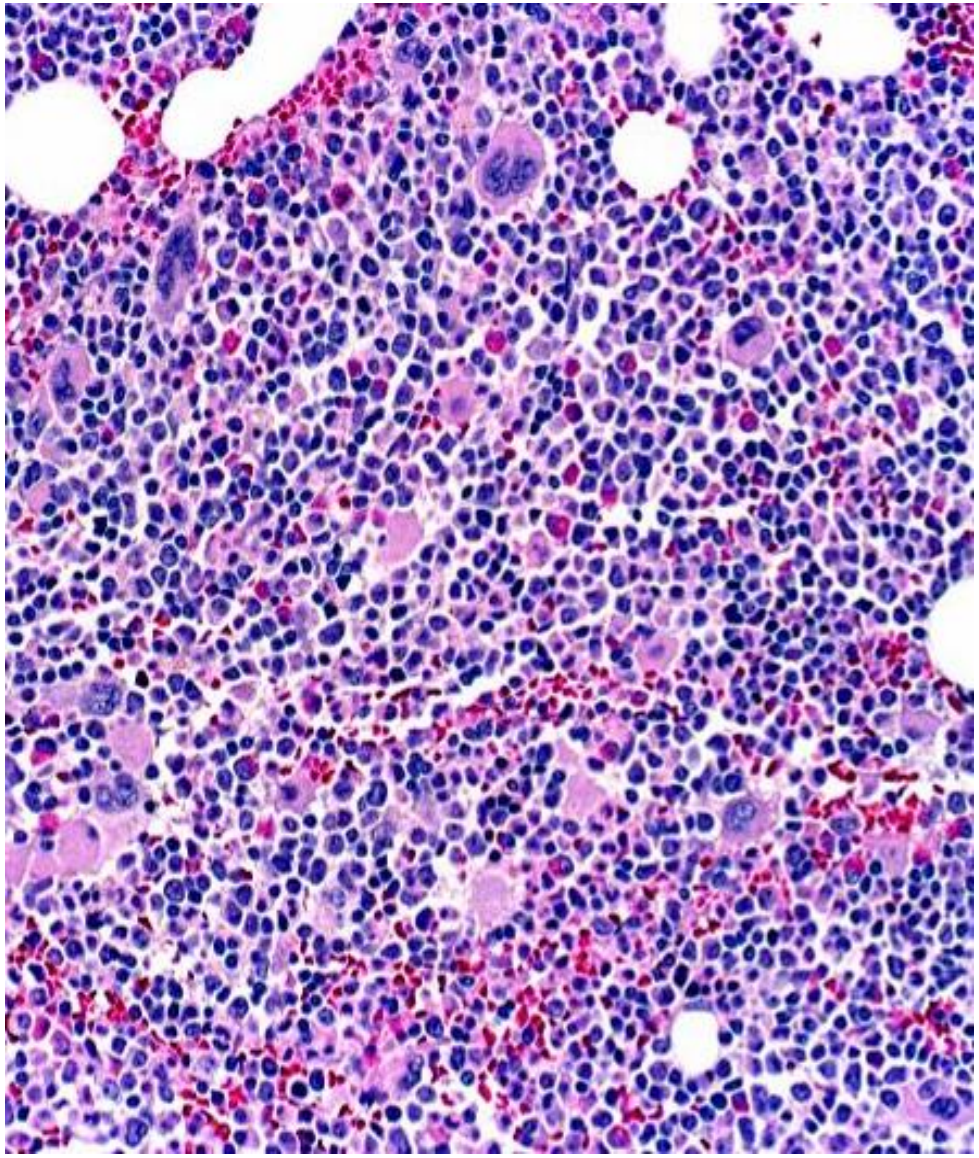
Blood

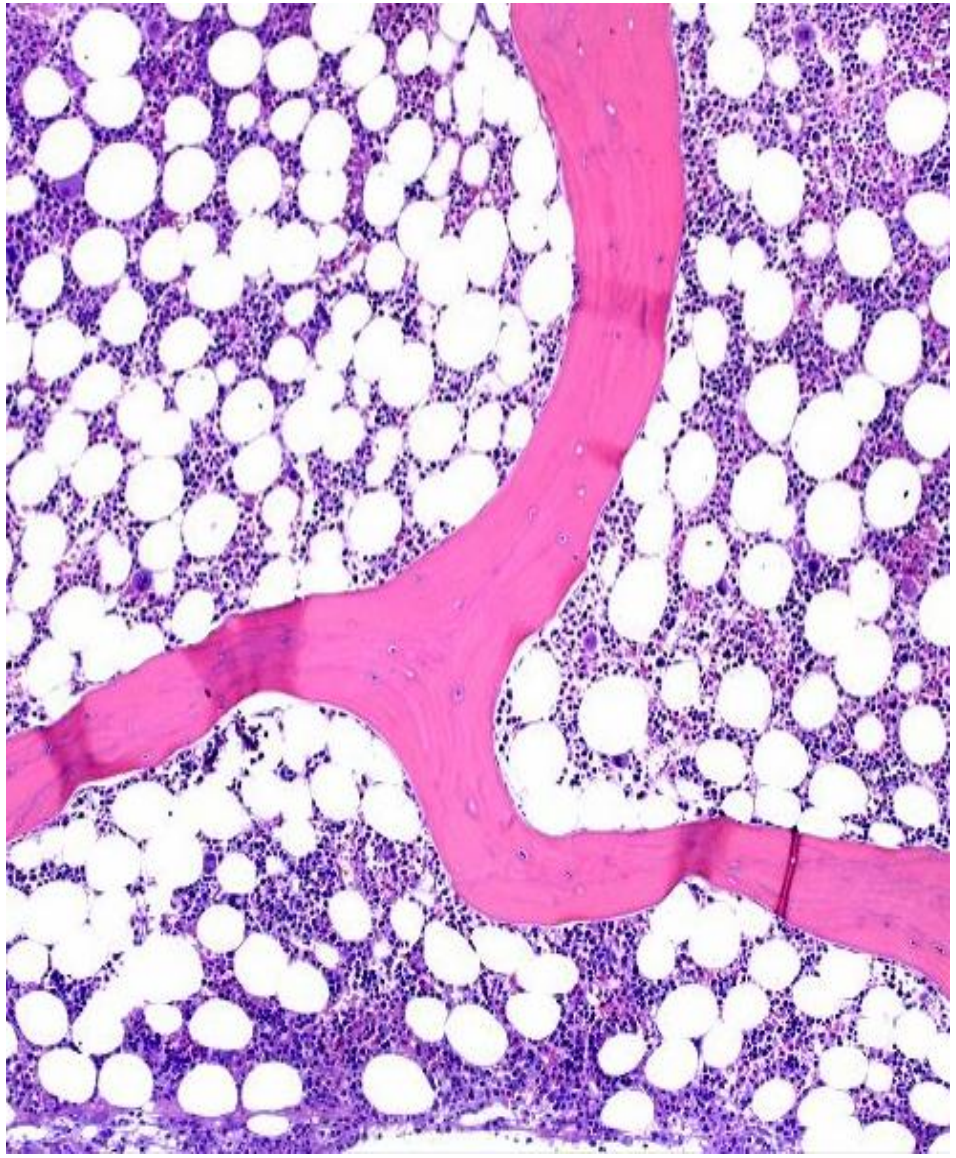
- Measures the protein your myeloma makes, not the myeloma itself
- Easy, repeatable, cheap, low risk
- Excellent for tracking a trend over months
- Blind to how much disease is sitting in the bone
- Nearly useless when the disease stops secreting protein

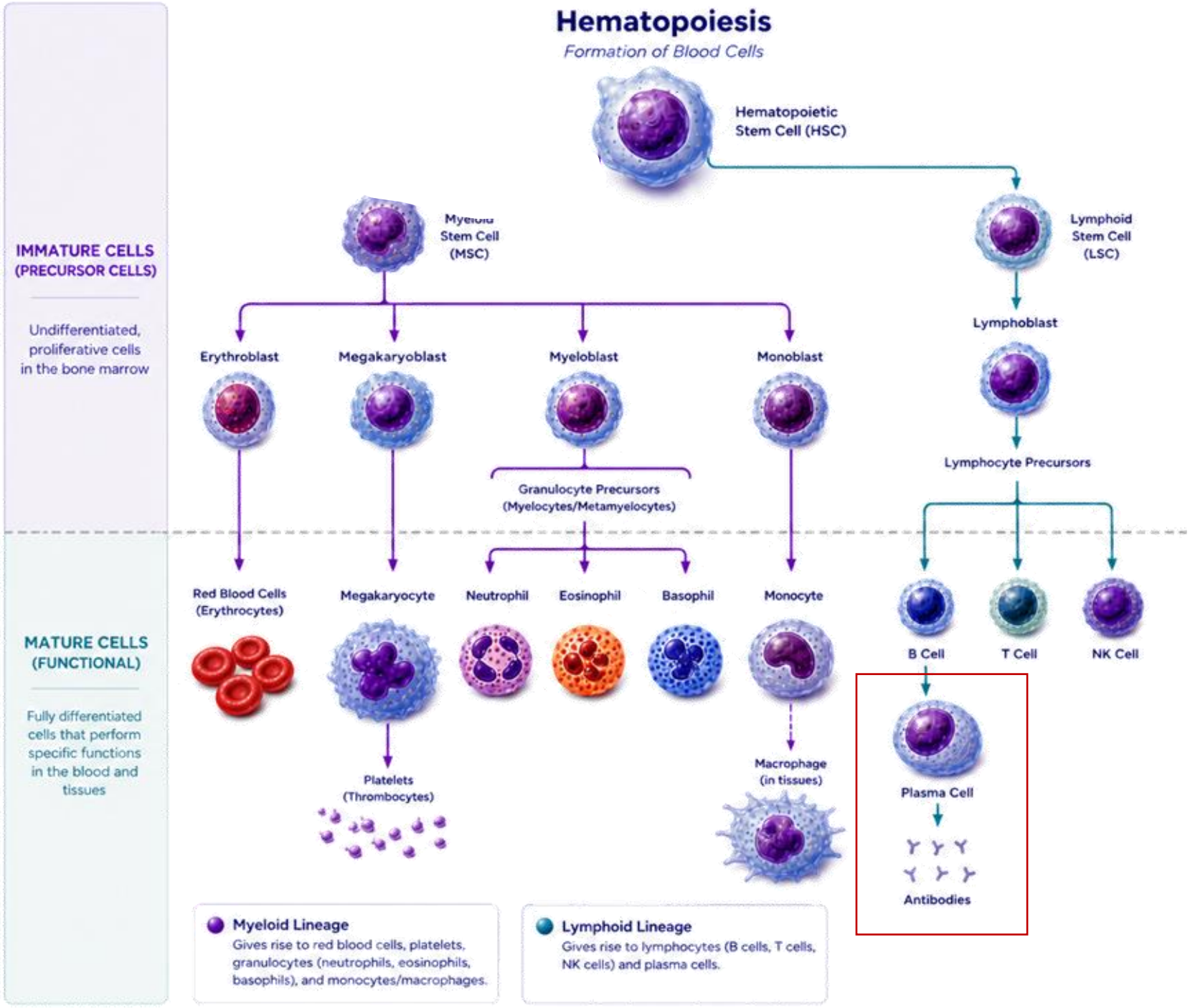
Marrow

- Measures the cells themselves
- The source for genetics, flow and MRD
- Gives percentage, pattern and architecture
- Invasive, so it is done at decision points, not monthly
- Samples one small site of a very large organ

Marrow is an organ roughly the size of your liver. Every biopsy is a keyhole view of it.







Plasma cell neoplasms

The procedure

1 Position and landmark

You lie on your side or face down. The site is the posterior iliac crest, the bony ridge at the back of the pelvis, chosen because the bone is thick and no important structures sit beneath it.

2 Skin and periosteum

Skin is cleaned and numbed. The deeper injection is aimed at the periosteum, the bone's outer lining, which is where nearly all of the sensation lives.

3 Aspirate first

A needle enters the marrow cavity and liquid marrow is pulled into a syringe. This pull is the brief deep ache people describe, and it lasts a few seconds.

4 Smears at the bedside

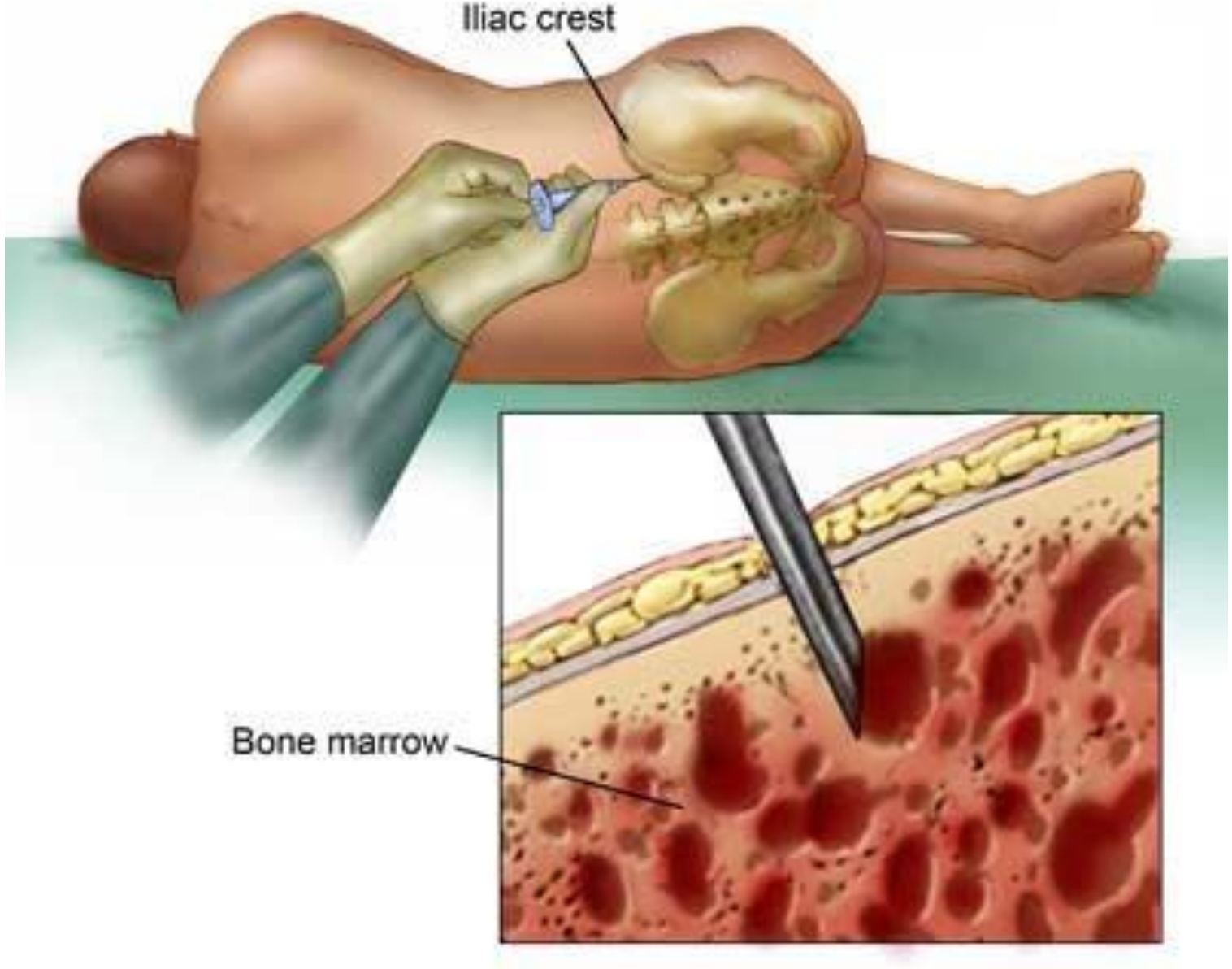
The first drops are spread onto glass slides right there in the room, because marrow clots within minutes and a clotted sample cannot be counted.

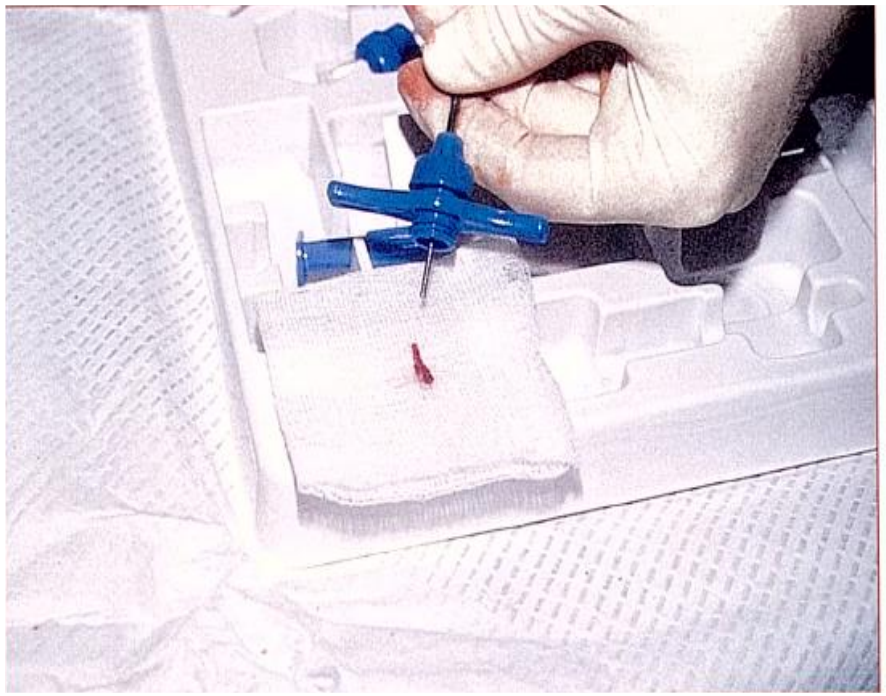
5 Core biopsy

A slightly larger needle takes a solid cylinder of bone, ideally one and a half to two centimeters long, so the structure of the marrow is preserved intact.

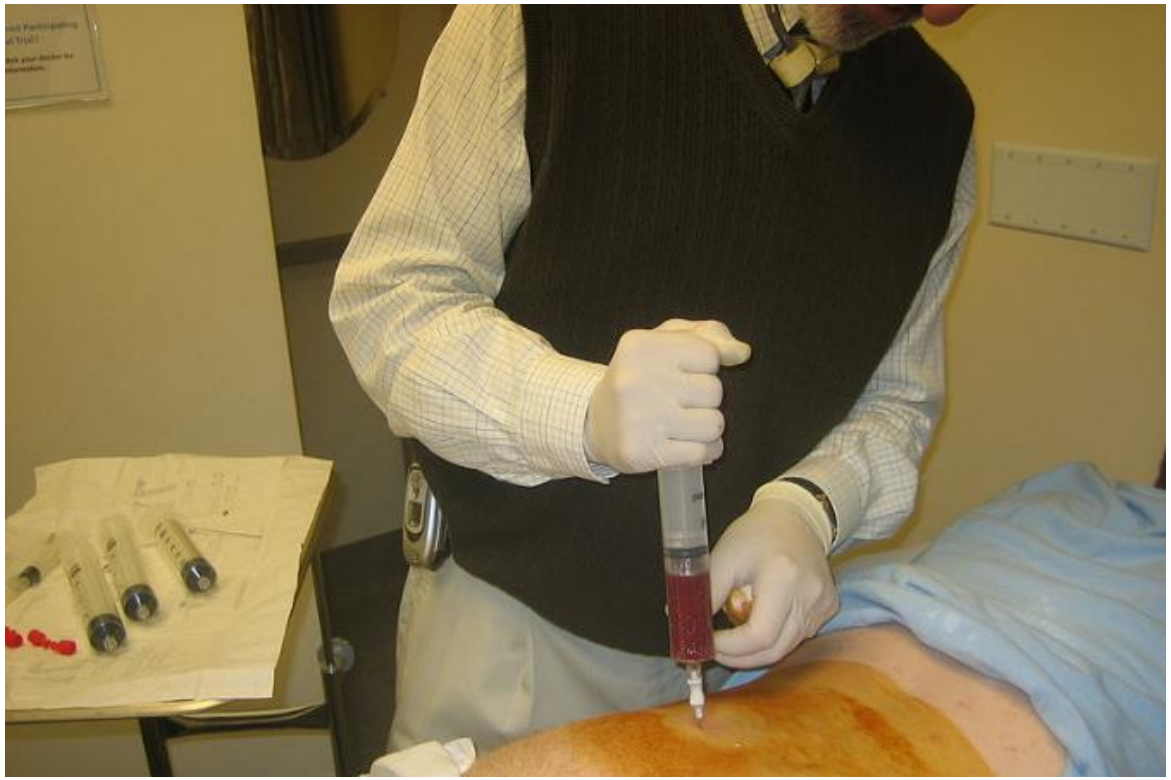
6 Touch preparations

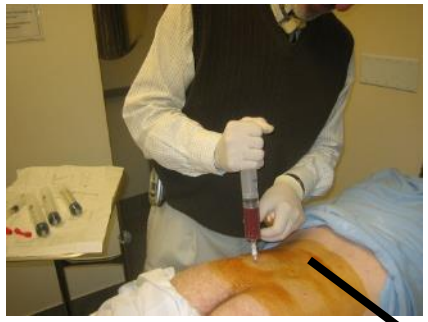
The core is rolled gently on a slide before it goes into fixative, giving a second look at cell detail even if the aspirate was poor.

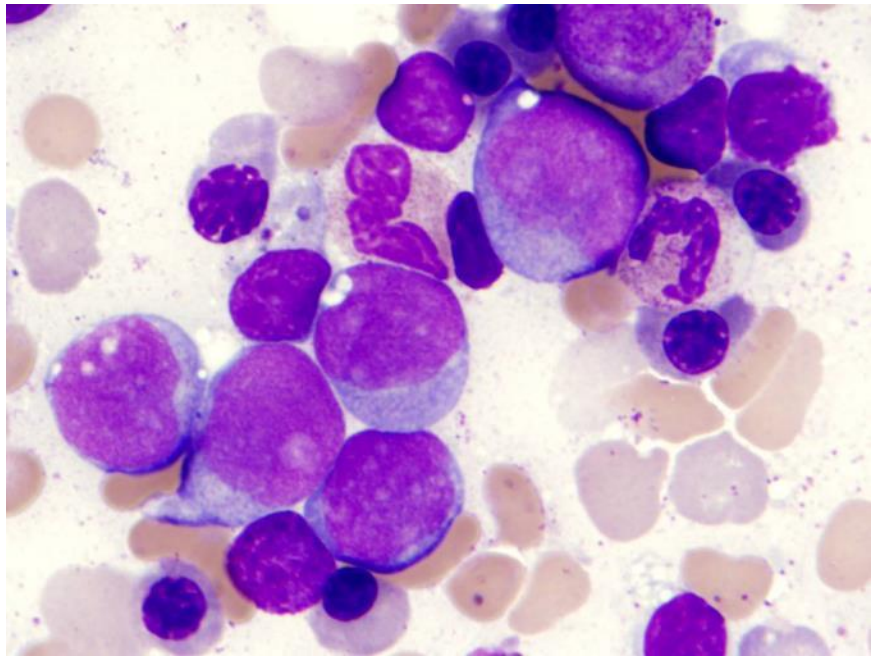

Iliac crest
Bone marrow




SPECIMEN



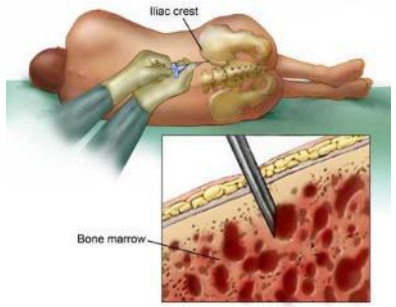




Flow cytometry

Molecular studies

Hematology Laboratory



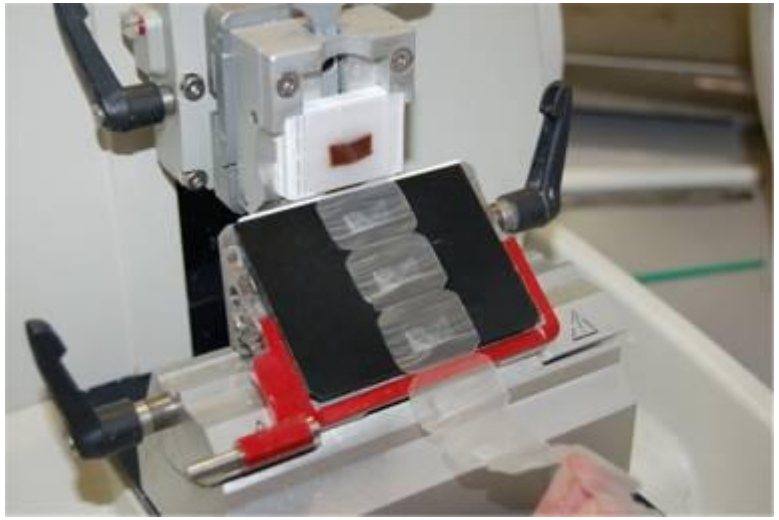
Formalin fixation

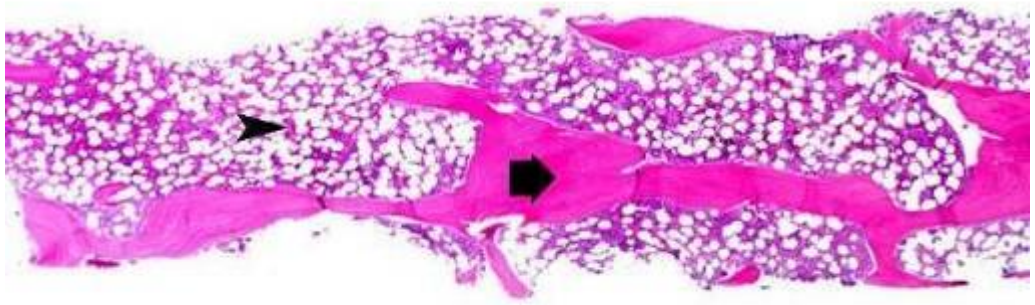
Surgical Pathology Gross Room

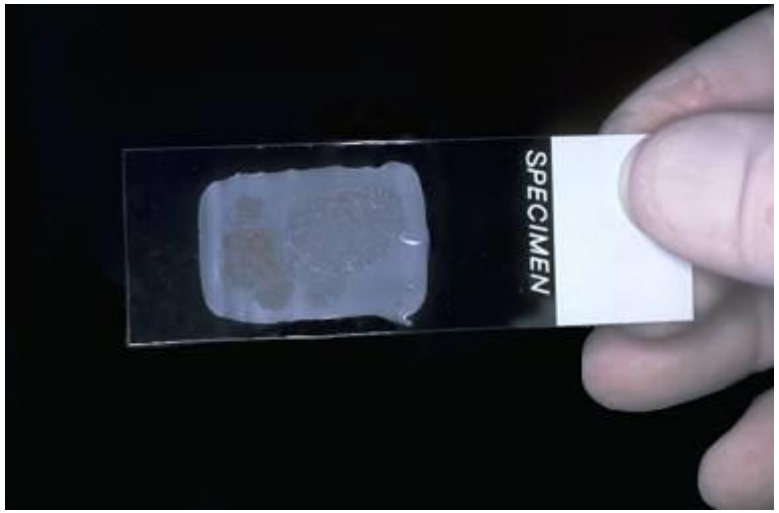
Decalcified 1.5 hours

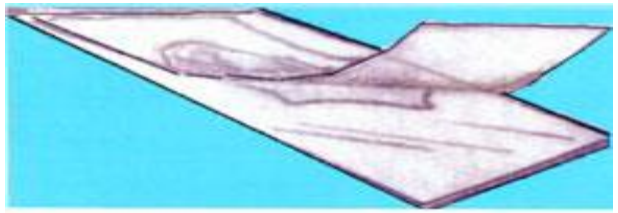
10% Neutral Buffered Formlin (NBF)

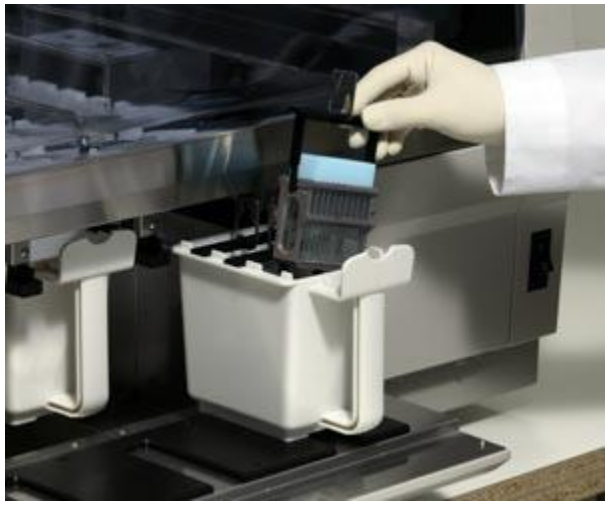
Paraffin Block

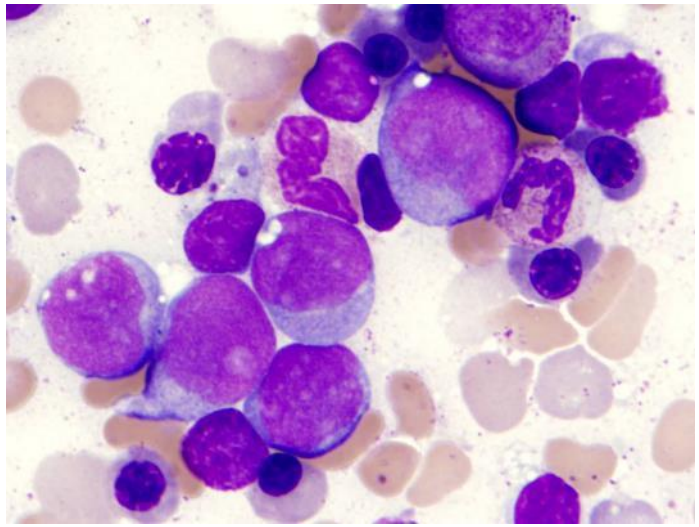
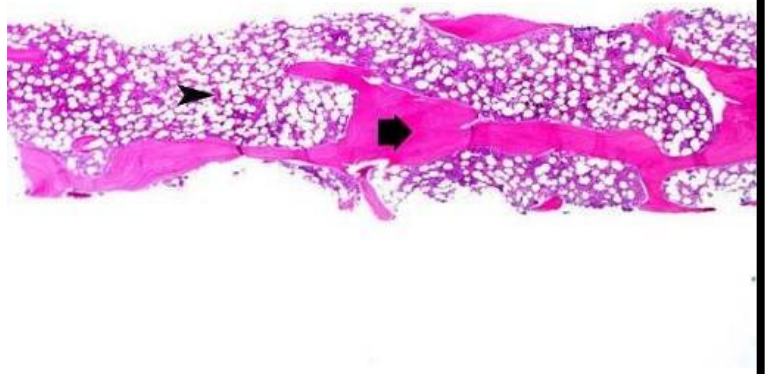


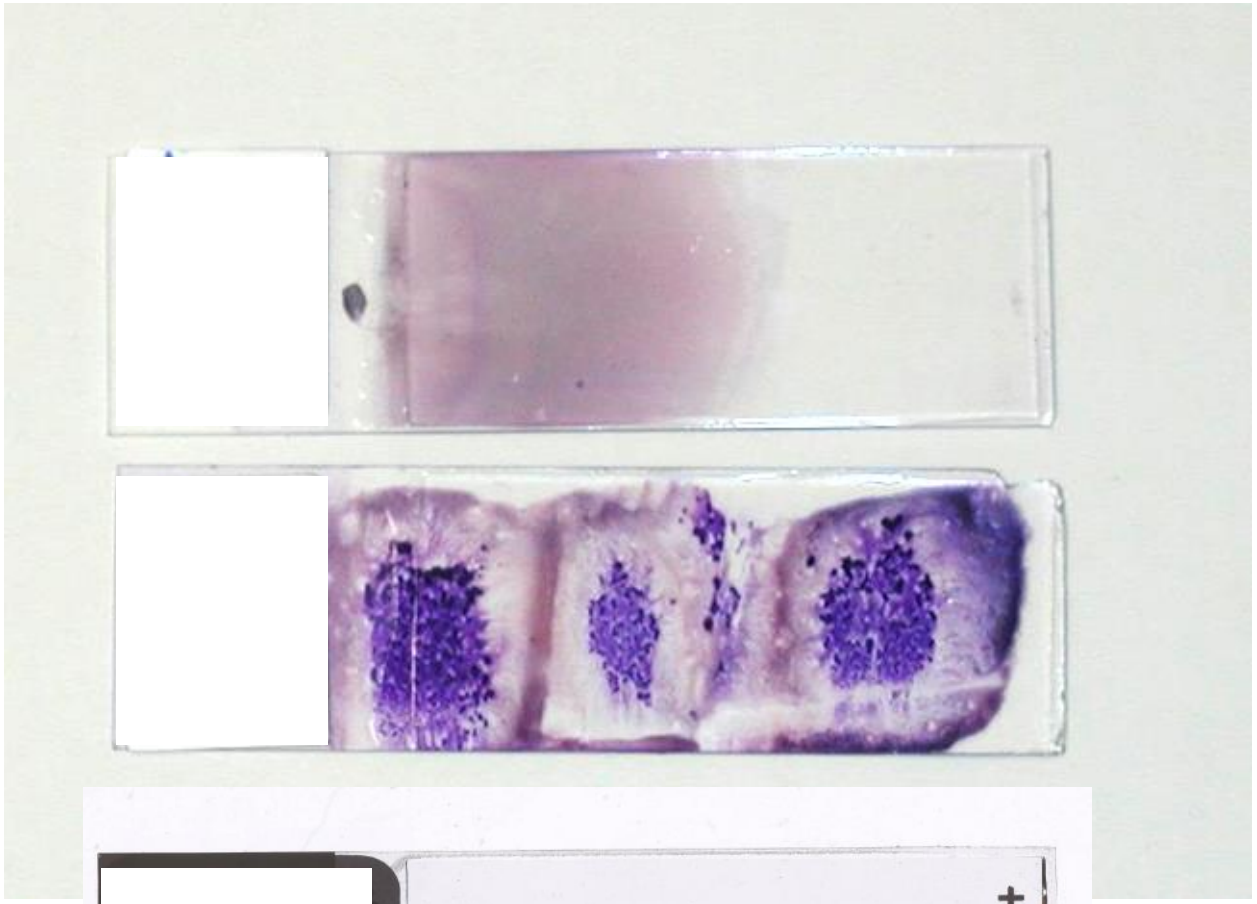



SPECIMEN





	Aspiration	Biopsy
Advantages	• Fast • Relative qty. of different cell types • Provides material for flow/molecular	• Ability to analyze cells and stroma • Represents all cells • Explains ‘dry’ taps
Drawbacks	Does not represent all cells	Slow processing
		


METRIC 1 2 3 4 5 6 7

WHAT ACTUALLY LEAVES THE ROOM

Four products from one procedure

Aspirate smears

Liquid marrow spread on glass. This is where the plasma cell percentage is counted, cell by cell, at high magnification.

The core biopsy

A cylinder of bone. This shows how full the marrow is, how the plasma cells are arranged, and whether they form sheets or clusters.

Tubes of liquid marrow

Sent live to other laboratories for flow cytometry, chromosomes, FISH and MRD. These tests need intact cells or intact DNA.

Clot section and touch preps

Backup material. When an aspirate is dry or a core is crushed, these often rescue the case and preserve the ability to stain.

ORDER OF THE DRAW

The first pull

The dilution problem

- Marrow sits in a sponge that is fed by blood vessels
- The first few milliliters are mostly true marrow
- Keep pulling and blood is drawn in behind it
- By the fourth or fifth pull, much of what enters the syringe is peripheral blood
- Diluted marrow lowers every percentage measured on it

First pull

Smears for morphology and the differential count

Early pulls

MRD sample, which needs the least diluted marrow available

Then

Flow cytometry, chromosomes and FISH

Last

Extra tubes, research and banking

A fair question for your team: which pull did my MRD sample come from?

BEHIND THE DOOR

The first forty eight hours in the laboratory

Every piece is logged, labeled and matched to you

The core sits in formalin so the cells stop changing

Acid or EDTA dissolves the mineral so the bone can be cut

Wax block, then slices thinner than a red cell

Color is added, then a human being looks at all of it

Why bone slows everything down

A core biopsy is bone, and bone cannot be sliced until the mineral is removed. That step alone runs from one hour to overnight depending on the method, which is the honest reason a marrow report takes days while a blood count takes minutes. The choice of method matters to you: strong acid decalcification is fast but chews up DNA, so a laboratory that may need molecular testing off the block will use a gentler agent and wait longer. When your report says the core was decalcified, that is not filler, it is the reason the timeline looks the way it does.

2

The microscope and the percentage

Where the number in your report is actually made

MORPHOLOGY

What a plasma cell looks like, and what myeloma changes

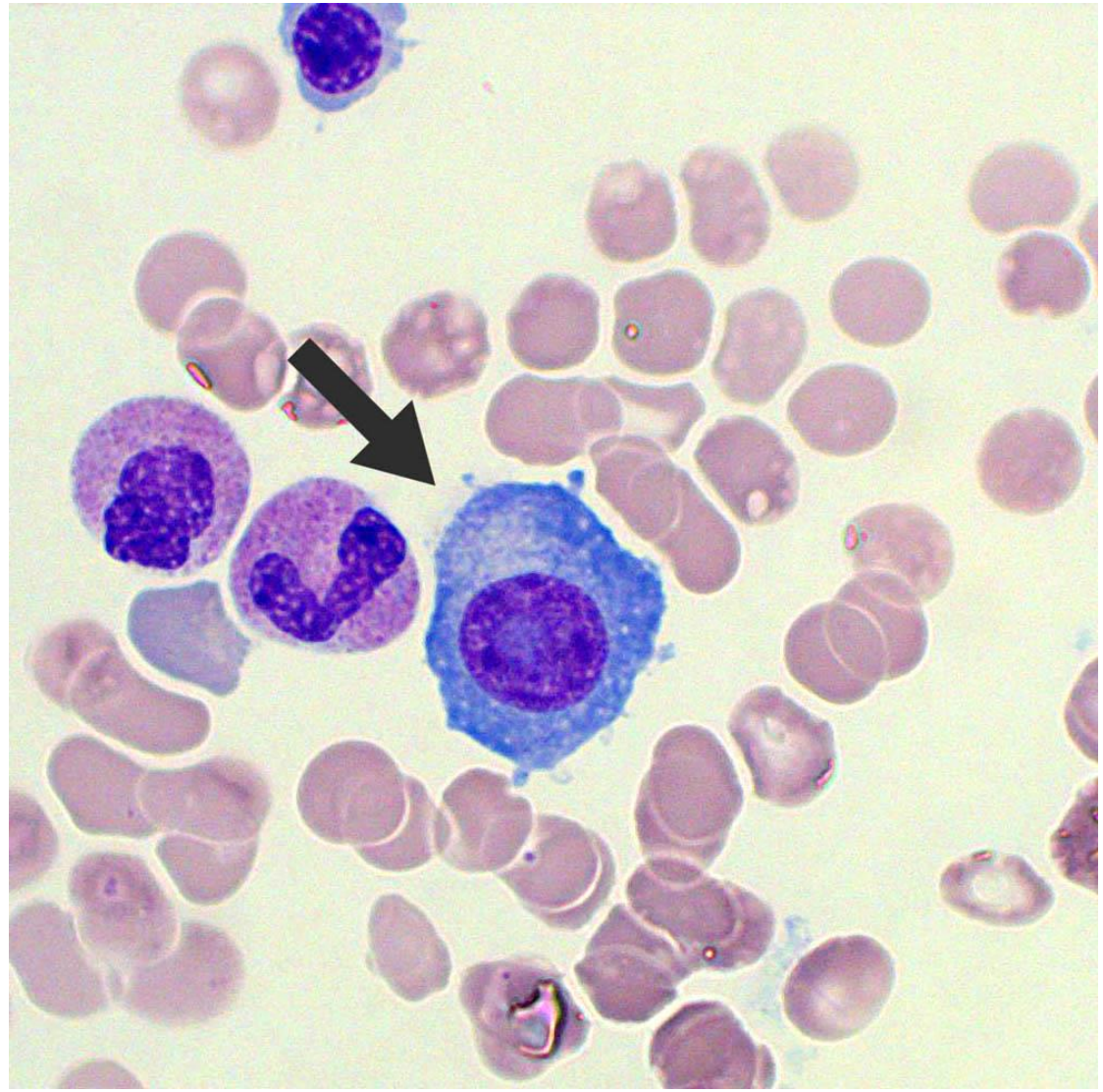
A normal plasma cell

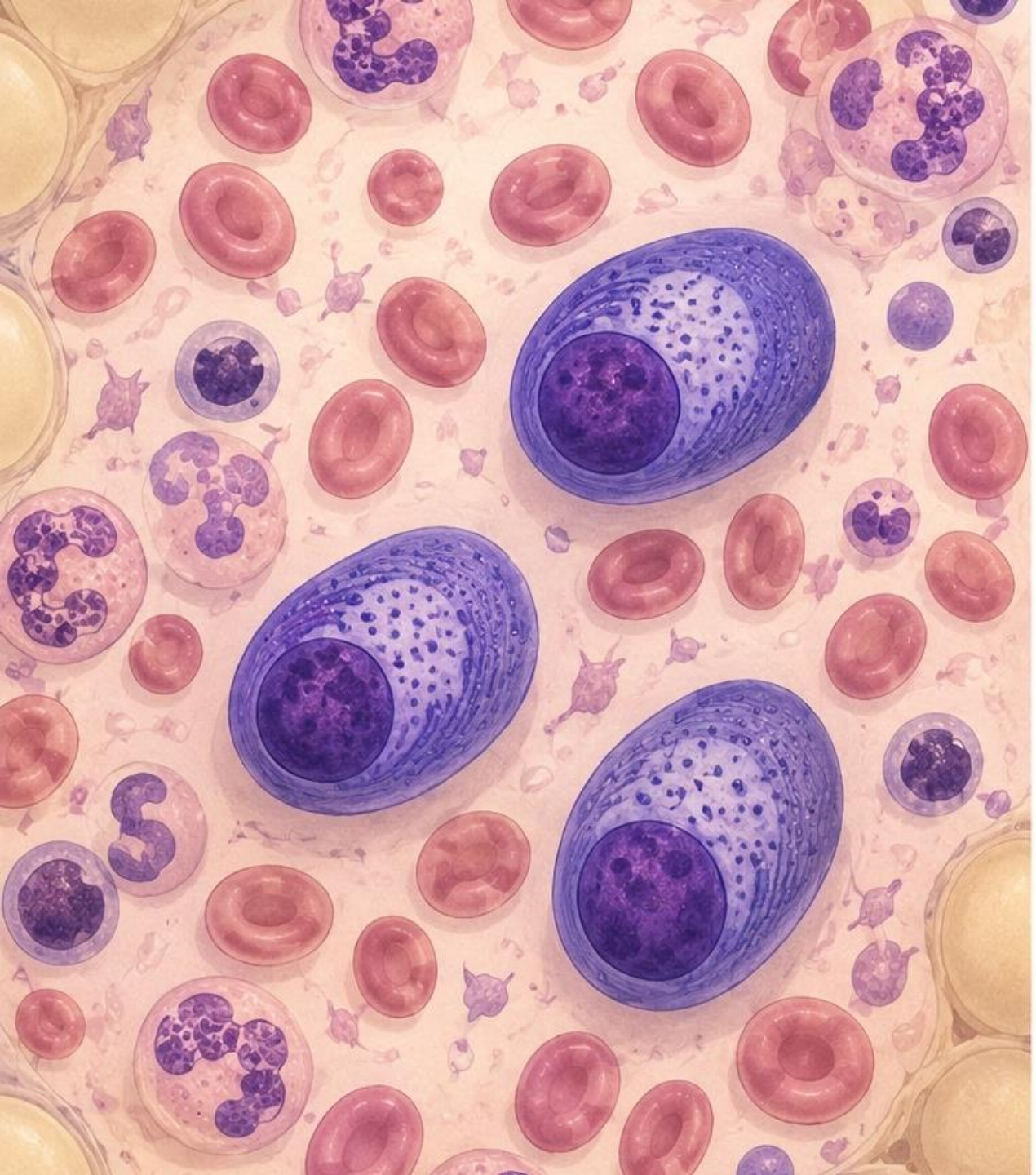
- An antibody factory in its final form
- Nucleus pushed to one side, like a clock face
- Deep blue cytoplasm, packed with protein machinery
- A pale zone beside the nucleus where antibody is packaged
- Normally one to three percent of marrow cells, scattered singly

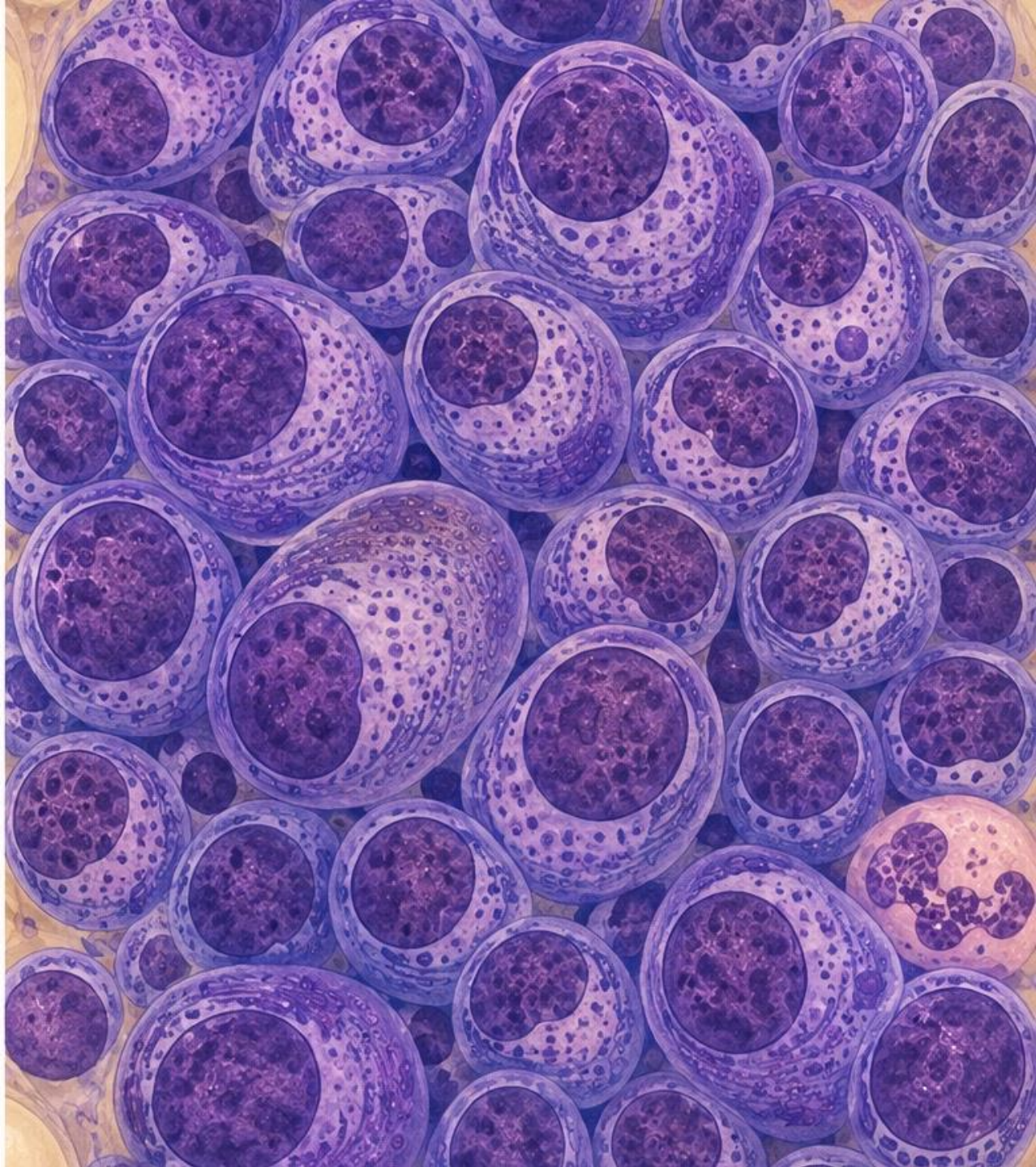
A myeloma marrow

- The same cell type, but far too many of them
- Arranged in sheets and clusters rather than singly
- Often larger, with prominent nucleoli and immature features
- Normal marrow elements crowded out, which is where the anemia comes from
- Appearance alone does not prove cancer; clonality does

Plasma cells increase in infection, autoimmune disease and inflammation as well







THE DIFFERENTIAL

How the percentage is actually counted

500

cells counted by hand, one at a time

1 in 500

equals 0.2 percent, the practical floor of what a count can resolve

What this means for your numbers

- A move from 40 percent to 45 percent is usually noise, not progression
- A move from 5 percent to 40 percent is signal, and no one needs statistics to see it
- Percentages are best read as trends across several time points, alongside your protein numbers
- Under about 5 percent, the count is no longer the right tool, and MRD testing takes over

TWO NUMBERS, ONE MARROW

Why the aspirate and the biopsy numbers may disagree

1	**The aspirate says 8 percent**	Liquid pulled from a sponge, diluted by blood, and myeloma cells that sit in fibrous tissue may not come out at all
2	**The core says 40 percent**	Solid tissue where nothing was diluted and nothing escaped, stained for CD138 so every plasma cell is visible
3	**Both numbers are correct**	They measure different things by different methods, and the difference is informative rather than an error
4	**The rule that applies**	International guidance uses the higher of the two, so the core often drives your diagnosis and your staging

TWO REQUIREMENTS, BOTH OF WHICH MUST BE MET

How myeloma is formally diagnosed

1 The cells

At least 10 percent clonal plasma cells in the marrow, or a plasmacytoma proven on biopsy

2 Plus a feature from SLiM or CRAB

CRAB means damage has already happened. SLiM means damage is coming soon enough to act now

SLiM: predicting damage

- S: sixty percent or more clonal plasma cells
- Li: involved to uninvolved free light chain ratio of 100 or more
- M: more than one focal lesion of at least 5 millimeters on MRI
- Any one of these alone converts smoldering disease into active myeloma

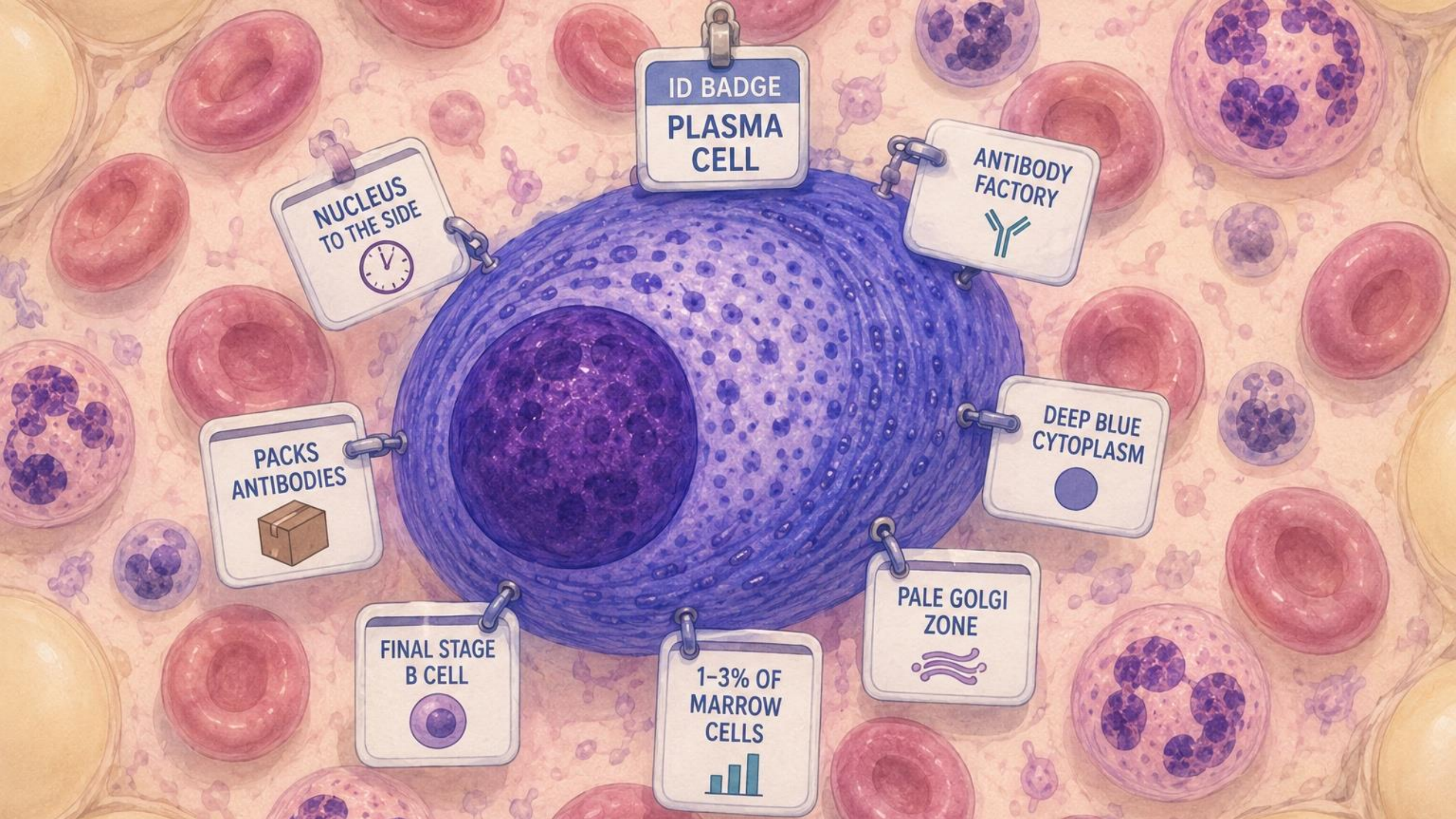
CRAB: damage already done

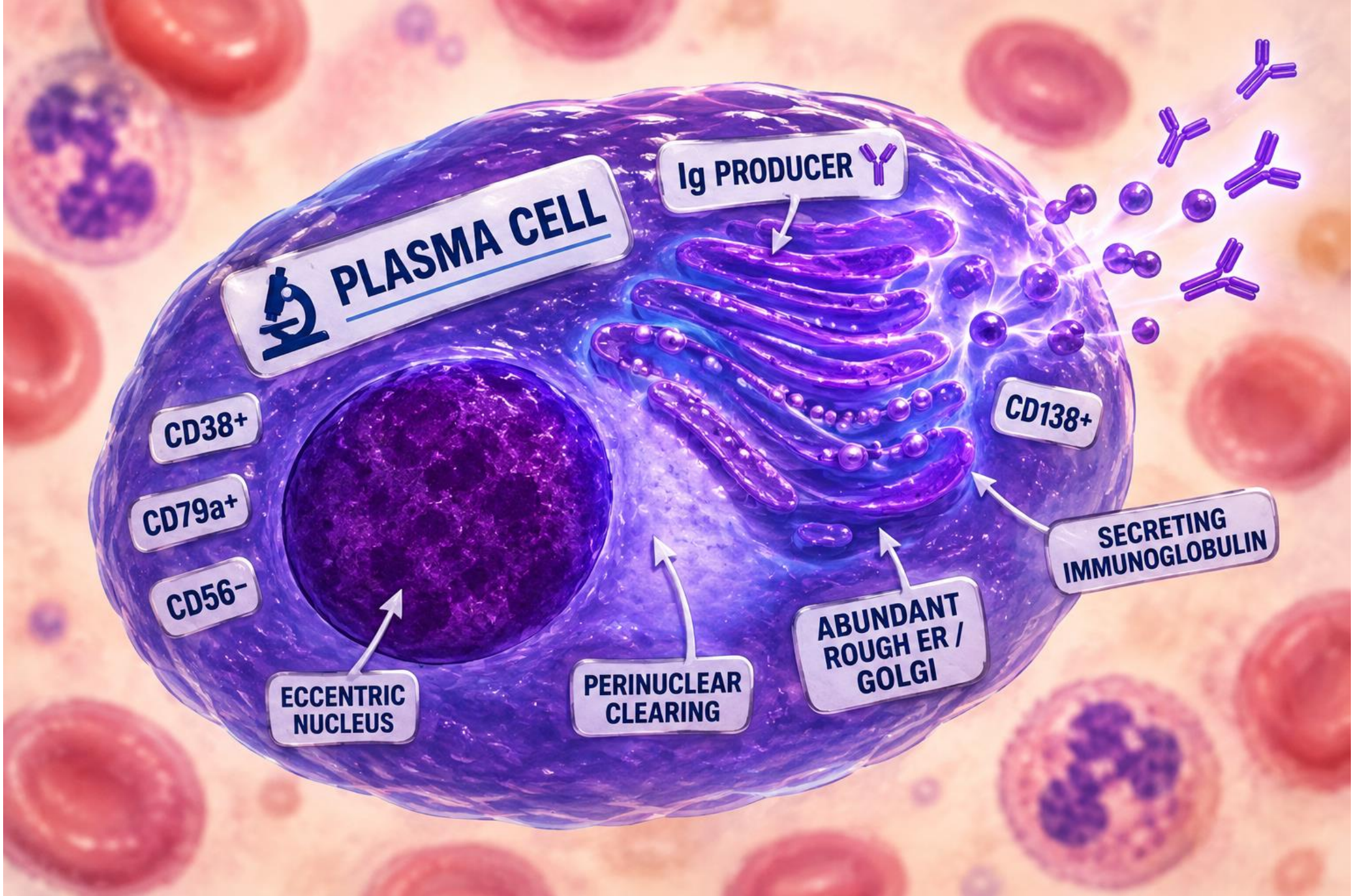
- Calcium raised in the blood
- Renal impairment
- Anemia
- Bone lesions or bone destruction
- Each must be attributable to the plasma cell clone rather than to something else

3

Stains and clonality

How color on a slide separates cancer from reaction


ID BADGE
PLASMA CELL
NUCLEUS TO THE SIDE
ANTIBODY FACTORY
PACKS ANTIBODIES
DEEP BLUE CYTOPLASM
FINAL STAGE B CELL
1–3% OF MARROW CELLS
PALE GOLGI ZONE


PLASMA CELL
Ig PRODUCER
CD38+
CD79a+
CD56−
CD138+
ECCENTRIC NUCLEUS
PERINUCLEAR CLEARING
ABUNDANT ROUGH ER / GOLGI
SECRETING IMMUNOGLOBULIN

The myeloma panel and what each marker means

CD138

The plasma cell marker. This is what the laboratory uses to find and count every plasma cell in the core.

CD38

Also marks plasma cells, and is the same target that daratumumab attacks, which is why it can vanish on treatment.

Kappa and lambda

The clonality test. One flavor of light chain in excess is the fingerprint of a single clone.

CD56

Present on many myeloma cells and absent on normal plasma cells, so it helps separate the two.

Cyclin D1

Turned on by the translocation between chromosomes 11 and 14, and a clue to a treatable subgroup.

CD19 and CD45

Normally present, typically lost in myeloma. Absence is as informative as presence.

If your report lists markers you do not recognize, that list is a reasonable thing to bring to a clinic visit.

Kappa and lambda: the actual cancer test

Normal marrow

Every antibody uses one light chain, either kappa or lambda. A healthy marrow contains a mixture from many independent plasma cells, running roughly two kappa for every one lambda. A mixture means many parents.

A myeloma marrow

Nearly every plasma cell shows the same light chain, because nearly every plasma cell descends from one ancestor. A single flavor means a single parent, and a single parent is what the word clone means.

Why this matters more than the percentage

A marrow can be full of plasma cells after a serious infection and be entirely benign, because those cells came from many different parents responding to many different targets. Restriction to one light chain is the finding that converts a crowded marrow into a diagnosis of cancer, and it is the same principle behind the serum free light chain ratio in your blood work and behind the DNA fingerprint used for MRD testing later in this talk.

Plasma Cell Dyscrasias

	MGUS	Asymptomatic (Smoldering) Myeloma	Symptomatic Myeloma	Amyloidosis	Waldenstrom Macroglobulinemia
Presentation	Monoclonal protein	Monoclonal protein	• Monoclonal protein • CRAB	Monoclonal protein • Macroglossia • Cardiomegaly • Carpal tunnel • "raccoon eyes" • Nephrotic syndrome	IgM monoclonal protein Lymphadenopathy Anemia Hyperviscosity
Diagnosis	• Normal count • Less than 10% clonal plasma cells in bone marrow	▪ No CRAB ▪ Greater than 10% clonal plasma cells in bone marrow	▪ CRAB ▪ Greater than 10% clonal plasma cells in bone marrow	• Congo red stain • Apple green birefringence	• Lymphoplasmacytic infiltrate in bone marrow or lymph node • MYD88 mutation
Other	No treatment	No treatment	Treat	Treat	• Treat if symptomatic • Is considered a low grade lymphoma

MGUS and Smoldering Myeloma are asymptomatic and do not require treatment, but require monitoring as they can progress to symptomatic myeloma.

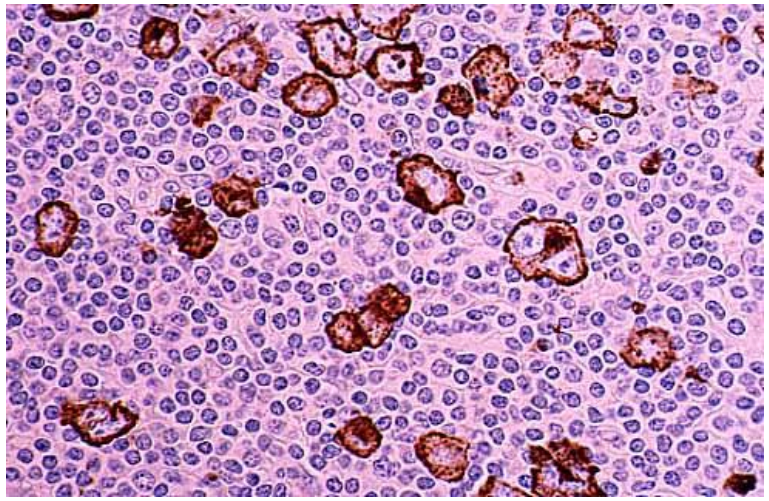
4

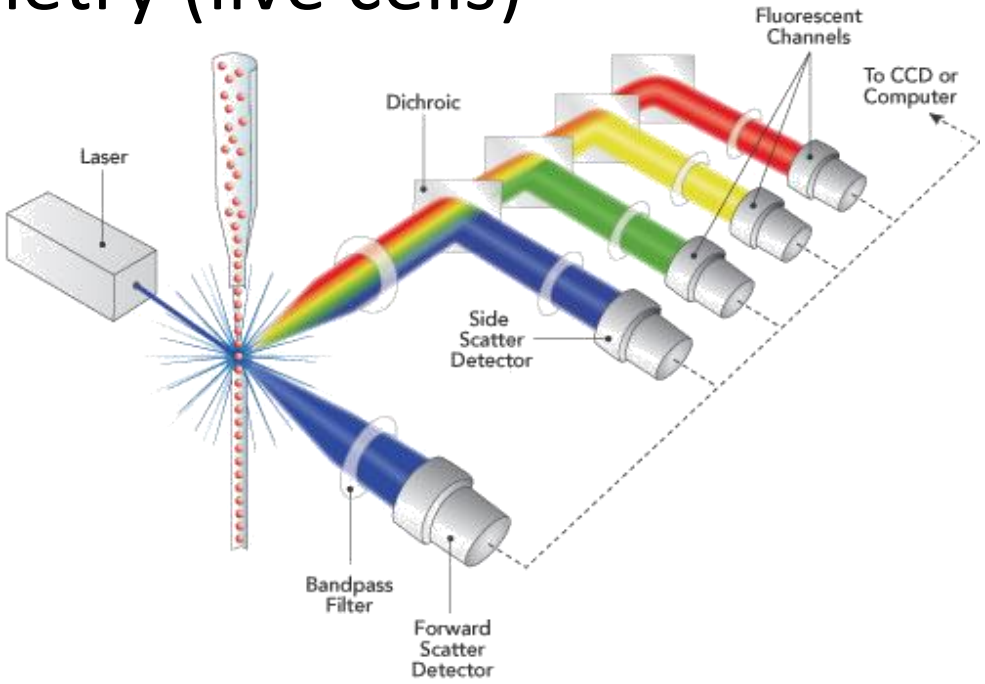
Flow cytometry

Lasers reading cells one at a time, thousands per second

Flow cytometry

- Study of what antigens a cell expresses
- “ID badge”
- On tissue → immunohistochemistry (fixed cells)
- On fluid → flow cytometry (live cells)

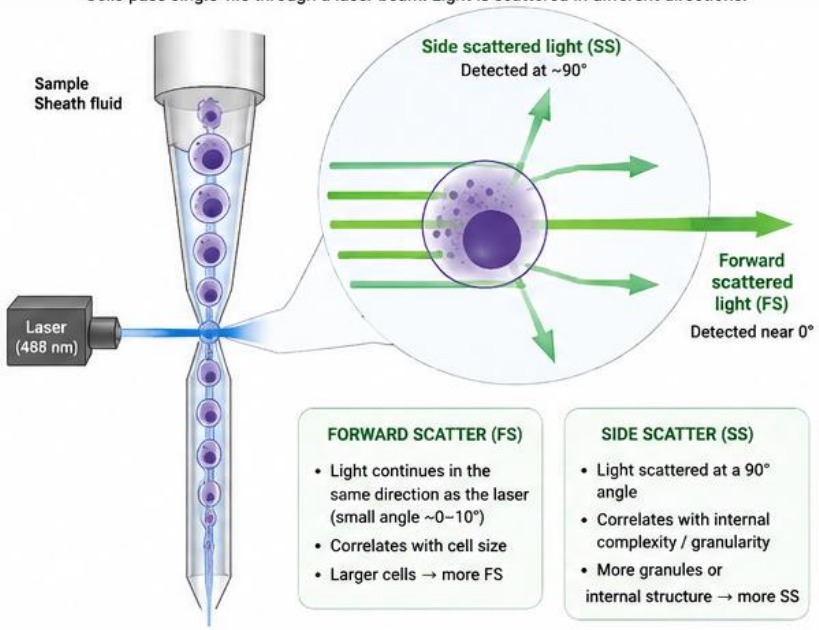




FLOW CYTOMETRY: HOW IT WORKS

1. HOW FORWARD SCATTER (FS) AND SIDE SCATTER (SS) WORK

Cells pass single-file through a laser beam. Light is scattered in different directions.



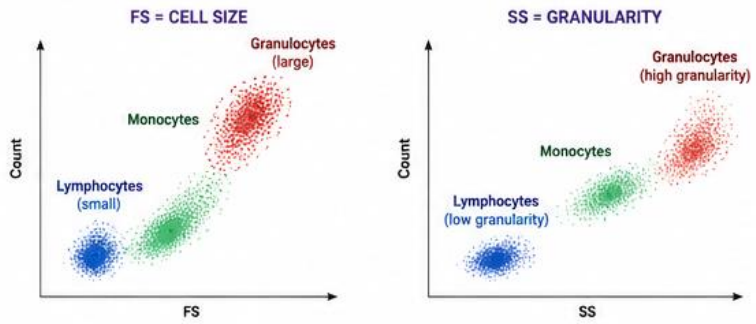
FORWARD SCATTER (FS)

- Light continues in the same direction as the laser (small angle ~0–10°)
- Correlates with cell size
- Larger cells → more FS

SIDE SCATTER (SS)

- Light scattered at a 90° angle
- Correlates with internal complexity / granularity
- More granules or internal structure → more SS

WHAT IT TELLS US

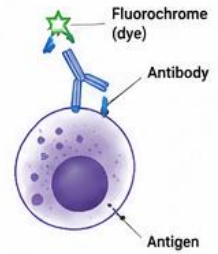


FS tells us HOW BIG the cell is.
SS tells us HOW COMPLEX (granular) the cell is.

2. HOW FLUORESCENT ANTIGENIES ARE ACTIVATED AND DETECTED

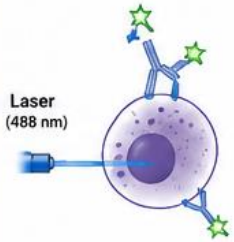
1 ANTIBODY BINDING

Fluorochrome-conjugated antibody binds specifically to its antigen on the cell surface or inside the cell.



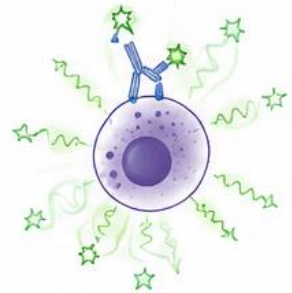
2 LASER EXCITATION

The laser light excites the fluorochrome when it hits the cell.



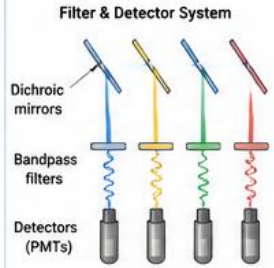
3 FLUORESCENCE EMISSION

The excited fluorochrome emits light at a longer wavelength (lower energy).



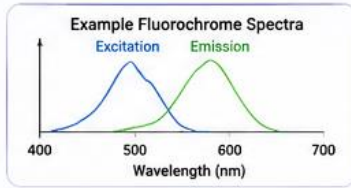
4 DETECTION

Filters (optical bandpass filters) separate the emitted light by wavelength and direct it to detectors (PMTs).



KEY POINTS

- Each fluorochrome has a specific excitation and emission spectrum.
- Dichroic mirrors reflect shorter wavelengths and transmit longer wavelengths.
- Bandpass filters allow only a narrow range of wavelengths to reach each detector.
- The intensity of the signal is proportional to the amount of antigen (more binding = brighter signal).



3. FROM SIGNALS TO DATA (PLOTS)

Each cell is measured for FS, SS, and fluorescence intensity in multiple channels.

ELECTRONIC SIGNALS

Detectors convert light into electrical signals.

DIGITAL CONVERSION

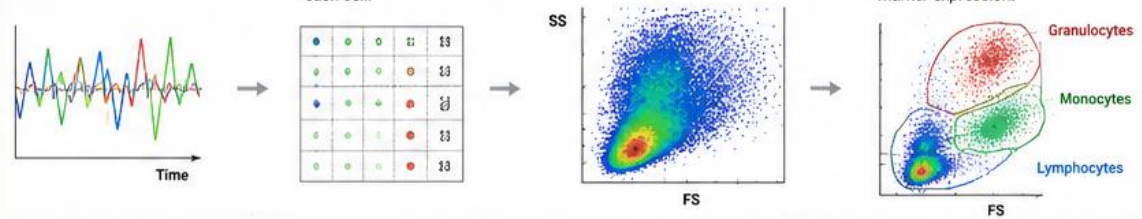
Signals are digitized and recorded for each cell.

DATA ANALYSIS

Thousands of cells are displayed on plots.

POPULATION IDENTIFICATION

Cells are gated into populations based on size, granularity, and marker expression.



STRENGTHS AND LIMITS

What flow tells us, and where it falls short

What it does well

- Separates abnormal plasma cells from normal ones within minutes
- Detects loss of CD19 and CD45 and gain of CD56, the aberrant pattern
- Reads light chain restriction inside the cell, one cell at a time
- Scales to ten million cells, which is what makes flow based MRD possible
- Available same day in most hospital laboratories

Where it falls short

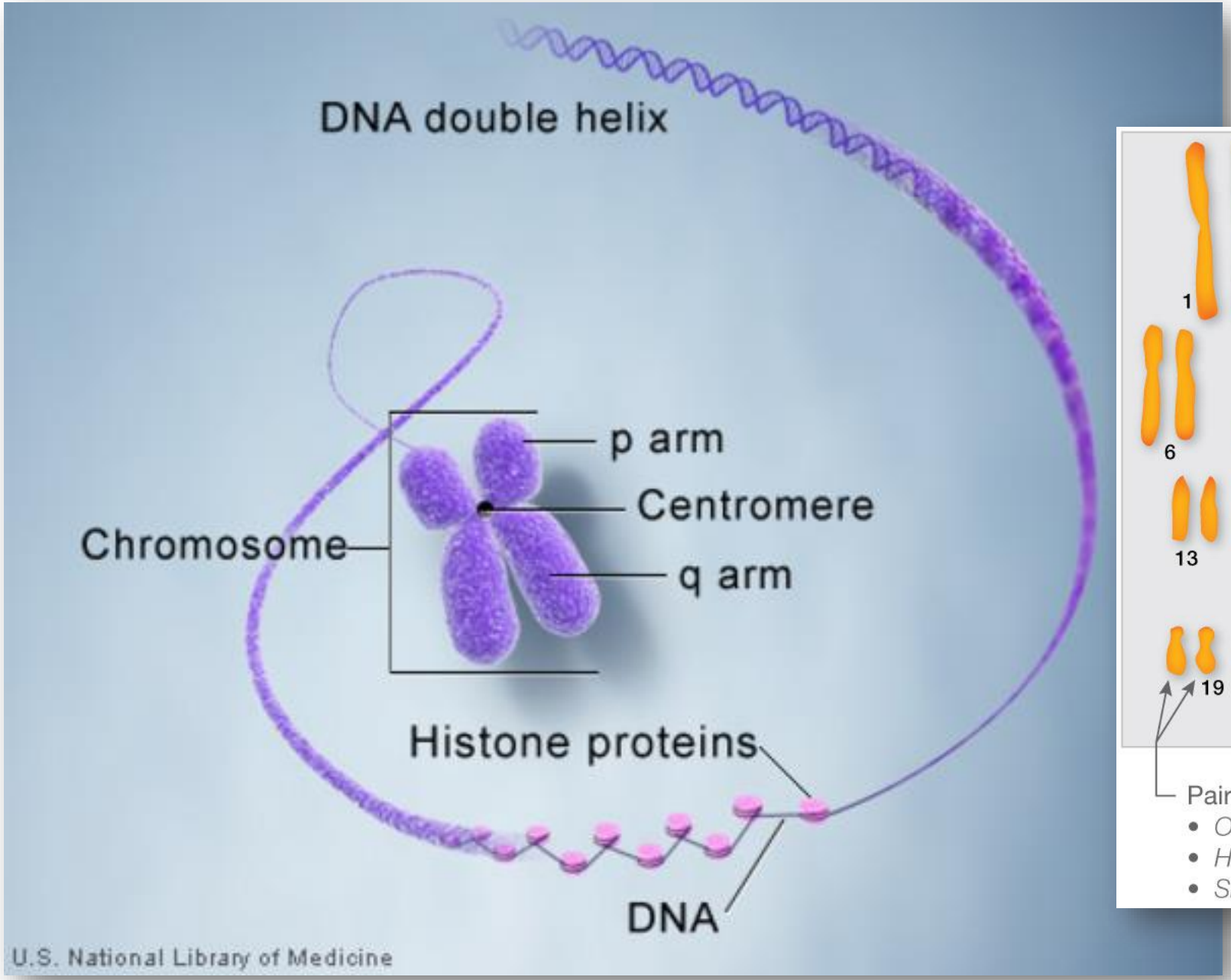
- Needs living cells, so the sample must reach the laboratory quickly
- Plasma cells are fragile and rupture during processing, so flow usually reports a lower percentage than the biopsy
- Blood dilution during the draw lowers the result directly
- Never use the flow percentage as your disease burden; that number belongs to the stained core

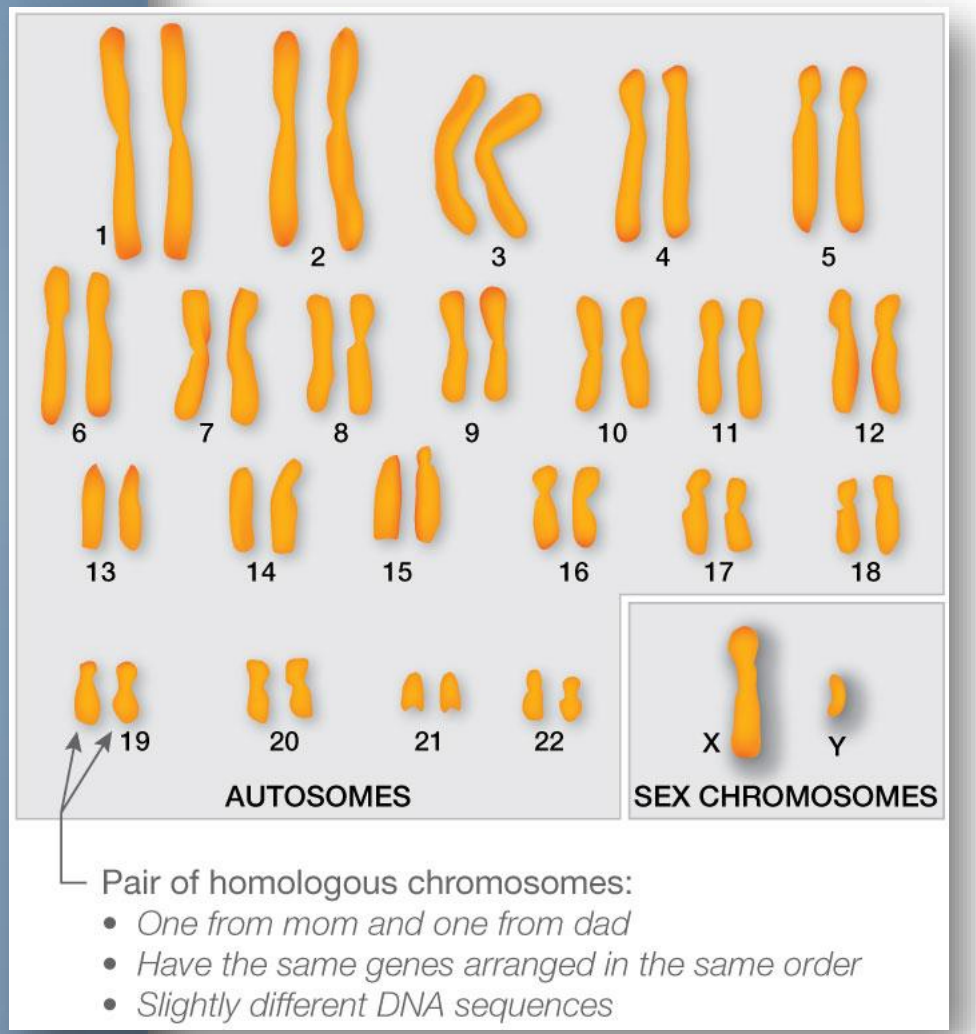
Three numbers, three methods, three different values. The report is supposed to reconcile them for you.

5

FISH and genetics

Where your risk category comes from, and why the sample has to be purified first


DNA double helix
p arm
Centromere
Chromosome
q arm
Histone proteins
DNA
U.S. National Library of Medicine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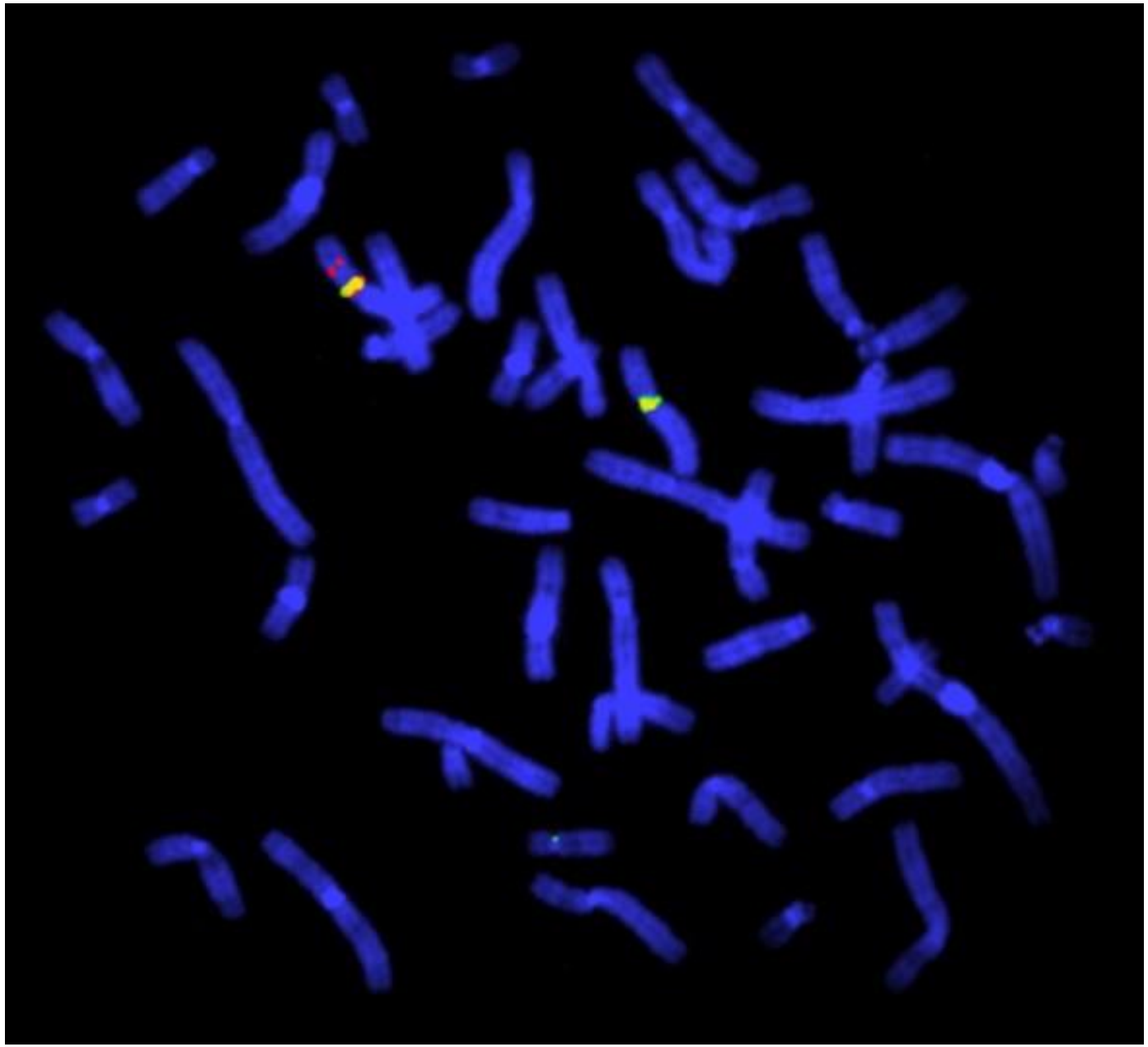
AUTOSOMES
X
Y
SEX CHROMOSOMES
Pair of homologous chromosomes:
One from mom and one from dad
Have the same genes arranged in the same order
Slightly different DNA sequences

What FISH is, in four steps

1	**Pick an address**	Choose the exact stretch of DNA in question, for example the site on chromosome 17 that carries TP53
2	**Build a probe**	Make a short piece of matching DNA and attach a fluorescent dye to it, red or green
3	**Let it find its match**	Applied to cells on a slide, the probe binds only to its complementary sequence and nothing else
4	**Count the dots**	Under a fluorescence microscope, two red dots is normal, one red dot means a piece is missing, fused colors mean two chromosomes have swapped material



The panel, and what the findings mean

Generally favorable

- Hyperdiploidy, meaning extra copies of whole chromosomes
- Translocation 11;14, which also flags a possible venetoclax option
- Absence of any high risk marker

Generally high risk

- Deletion of 17p, the loss of the TP53 safety brake
- Translocation 4;14
- Translocation 14;16 and 14;20
- Gain or amplification of 1q21

Context matters

- Risk is a probability across populations, not a prediction about you
- Categories have shifted repeatedly as treatment improved
- Two or more high risk markers together carry more weight than one

High risk genetics describes how the disease is likely to behave, not how you will do. People with high risk markers achieve deep remissions every day, and the label exists to inform intensity of treatment rather than to set an expectation.

6

MRD and clonoSEQ

Finding one cancer cell among a million normal ones, and the questions you sent me

What measurable residual disease means

1 in 20

what a microscope can resolve

1 in 100,000

routine MRD sensitivity, written as ten to the minus five

1 in 1,000,000

best available sensitivity, ten to the minus six

Why the field went looking below the microscope

- Complete remission once meant a normal marrow under the lens, and people still relapsed
- Complete remission by that definition was hiding an enormous range of actual disease burden
- Depth of response measured below the microscope tracks with how long remissions last
- MRD is now used as a trial endpoint, and increasingly to inform how long treatment continues

Two technologies, two completely different approaches

Next generation flow

- Looks at cells, ten million of them, one at a time
- Needs fresh living cells within hours
- No baseline sample required, so it can be started at any point
- Results in a day, often in the same hospital
- Reaches ten to the minus five, and ten to the minus six with a strong sample
- Depends heavily on local expertise and standardization

Next generation sequencing

- Looks at DNA, not at cells, and never images anything
- Works on shipped material, so it does not need a local laboratory
- Requires a baseline diagnostic sample to identify your clone first
- Results in roughly a week from a central laboratory
- Reaches ten to the minus six with adequate DNA input
- Highly standardized, since every sample runs in one place

THE IDENTIFICATION SAMPLE

clonoSEQ step one: building your fingerprint

1 Start with disease

A diagnostic marrow sample with plenty of myeloma cells is required, usually from the original workup. This step cannot be done in remission, because the clone has to be present to be found.

2 Amplify the antibody genes

Every B cell rearranges its antibody genes into a unique combination early in life. Multiplex PCR copies these regions from all the cells in the sample at once.

3 Sequence everything

The copied fragments are read on a sequencer, generating millions of reads. Most come from ordinary immune cells and represent millions of different sequences.

4 Find the one that dominates

In a myeloma marrow, one sequence appears far more often than any other, because it belongs to one clone. That dominant sequence is recorded as your tracking marker, and it is yours alone.

THE FOLLOW UP SAMPLES

clonoSEQ step two: tracking, and what the number means

What happens to each new sample

DNA is extracted from your marrow, the same antibody gene regions are amplified and sequenced, and software counts how many reads match your recorded sequence against the total number of cells the DNA represents.

Why sample size decides sensitivity

To claim one in a million, the laboratory must actually examine DNA from more than a million cells. That takes several milliliters of good marrow. A thin or diluted sample lowers the sensitivity that can be reported, and the report will say so.

Reading your MRD result properly

- The result is a count of cancer cells per million cells examined, not a percentage of anything familiar
- Negative always carries a sensitivity attached to it, so negative at ten to the minus five and negative at ten to the minus six are different statements
- Negative means nothing was found at that depth. It does not mean nothing is there
- Sustained negativity across time points carries far more weight than any single result

HONEST LIMITS

What MRD does not tell you

It is still a keyhole

MRD is measured in one small aspirate from one iliac crest. Myeloma is patchy, and disease elsewhere in the skeleton is invisible to that sample.

Disease outside the marrow

Extramedullary disease is not sampled by a marrow draw at all, which is why imaging remains part of the assessment rather than an optional extra.

Negative is not cured

A negative result at one in a million still leaves room for disease below that level. It is a very good sign and it is not a guarantee.

Not yet a universal switch

Using MRD to stop or de escalate treatment is an active research question. Trials are answering it now, and the answer will not be identical for everyone.

7

The blood work

The numbers you see every month, and what each one is really measuring

BLOOD TESTS

The monthly panel, decoded

Complete blood count

Red cells, white cells and platelets. The anemia in myeloma comes from marrow being crowded out, and this is where it shows first.

Serum protein electrophoresis

Separates blood proteins by electrical charge. Your M spike is the sharp peak where a single clone's product piles up.

Immunofixation

Identifies exactly which antibody type the clone makes. More sensitive than the spike, and often the last thing to become negative.

Free light chains

Measures the loose light chains circulating without a partner. The ratio between kappa and lambda is the number that matters, not either one alone.

Beta 2 microglobulin

A protein shed by cells that reflects tumor burden and kidney function together. One of the two original staging numbers.

Chemistry panel

Calcium, creatinine, albumin and LDH. These are the numbers that describe what the disease is doing to the rest of you.

CRAB, and what response categories mean

CRAB: the damage the disease does

- Calcium raised, released as bone breaks down
- Renal impairment, most often from light chains injuring the tubules
- Anemia, from marrow crowded out by plasma cells
- Bone lesions, the holes seen on imaging
- Any one of these attributable to the clone means active disease requiring treatment

Response, from shallow to deep

- **Partial response:** protein down by at least half
- **Very good partial response:** down by at least ninety percent, or detectable only by the sensitive method
- **Complete response:** no clone detectable in blood or urine by immunofixation, and under five percent plasma cells in marrow
- **Stringent complete response:** complete response plus a normal light chain ratio and no clonal cells on staining
- **MRD negative:** nothing found at one in a hundred thousand or one in a million

8

One family of diseases

MGUS, smoldering, myeloma, plasmacytoma, light chain disease, amyloidosis and plasma cell leukemia

Plasma Cell Dyscrasias

	MGUS	Asymptomatic (Smoldering) Myeloma	Symptomatic Myeloma	Amyloidosis	Waldenstrom Macroglobulinemia
Presentation	Monoclonal protein	Monoclonal protein	• Monoclonal protein • CRAB	Monoclonal protein • Macroglossia • Cardiomegaly • Carpal tunnel • "raccoon eyes" • Nephrotic syndrome	IgM monoclonal protein Lymphadenopathy Anemia Hyperviscosity
Diagnosis	• Normal count • Less than 10% clonal plasma cells in bone marrow	▪ No CRAB ▪ Greater than 10% clonal plasma cells in bone marrow	▪ CRAB ▪ Greater than 10% clonal plasma cells in bone marrow	• Congo red stain • Apple green birefringence	• Lymphoplasmacytic infiltrate in bone marrow or lymph node • MYD88 mutation
Other	No treatment	No treatment	Treat	Treat	• Treat if symptomatic • Is considered a low grade lymphoma

MGUS and Smoldering Myeloma are asymptomatic and do not require treatment, but require monitoring as they can progress to symptomatic myeloma.

SAME CELL, DIFFERENT AMOUNTS, DIFFERENT CONSEQUENCES

The spectrum, from watchful waiting to emergency

MGUS

Under 10 percent plasma cells, a small monoclonal protein, no organ damage. Not cancer. Monitored with blood tests.

Smoldering

Between 10 and 60 percent plasma cells and more protein, but still no CRAB or SLiM feature. Monitored closely.

Myeloma

At least 10 percent plasma cells plus a SLiM or CRAB feature. The malignant, treatable form of the same process.

Plasmacytoma

One localized tumor of plasma cells, in bone or in soft tissue, without widespread marrow disease.

Plasma cell leukemia

Large numbers of plasma cells circulating in the bloodstream. Rare, aggressive and treated promptly.

Every one of these begins in a single plasma cell that shuffled its antibody genes and then refused to stop dividing. What separates them is how many descendants there are, where those descendants sit, and whether the protein they make is harming an organ.

Light chain disease and non-secretory myeloma

Light chain myeloma

The clone makes light chains only, never assembling a complete antibody. Protein electrophoresis can look nearly normal because there is no large intact molecule to form a tall spike. The free light chain assay and urine testing become the instruments that matter, and the light chains themselves are what injure the kidney.

Non-secretory myeloma

A rare form in which no monoclonal protein is detectable in blood or urine at all. The diagnosis and the follow up rest on the marrow and on imaging rather than on a number that can be drawn from a vein. Some of these cases still make light chains that the sensitive assay can find, which is worth checking.

Why this changes how you are followed

Your monitoring plan is built around whatever your particular disease actually secretes. Someone with a large IgG spike can be followed largely on electrophoresis, someone with light chain disease is followed on the free light chain ratio, and someone with non-secretory disease is followed with marrow examinations and imaging on a schedule. If you have ever wondered why your neighbor in this group gets different tests at different intervals, this is usually the reason.

THE TWO ENDS OF THE SAME DISEASE

Plasmacytoma and plasma cell leukemia

Plasmacytoma: disease in one place

- A single localized tumor made of clonal plasma cells
- Solitary plasmacytoma of bone when it sits inside bone, extramedullary when it sits in soft tissue
- A true cancer, but confined rather than spread through the marrow
- Usually treated with radiation, sometimes surgery, and it often responds very well
- Blood, urine and imaging studies are done to rule out myeloma, and follow up continues because some progress later

Plasma cell leukemia: disease everywhere

- Large numbers of clonal plasma cells circulating in the blood itself
- Found on an ordinary blood smear and confirmed by flow cytometry
- Primary when it appears at diagnosis, secondary when it emerges late in established myeloma
- Rare and aggressive, and treatment begins promptly rather than after further observation
- One of the few settings where a routine blood smear changes management the same day

AL amyloidosis: when the protein is the problem

What is actually happening

The light chains made by the clone misfold and lock together into fibers the body cannot clear. Those fibers deposit in organs, and the organ stiffens and fails. The number of plasma cells may be modest while the illness is severe, because here the damage is done by the protein rather than by the cells.

Where it shows up

Heart, causing thickening and failure. Kidney, causing protein loss and swelling. Nerves, causing numbness. Liver, tongue and soft tissue as well. It can occur on its own, alongside MGUS, or together with myeloma, which is why the marrow is examined even when the presenting problem looks purely cardiac.

In myeloma the burden of disease and the severity of illness usually track together. In amyloidosis they come apart completely, and a patient with a plasma cell percentage that would be called unremarkable can be in heart failure. Anyone in this room with unexplained swelling, breathlessness, protein in the urine or a newly enlarged tongue in the setting of a monoclonal protein should have amyloidosis raised explicitly with their team rather than waiting for it to be considered.

How amyloid is found and typed

1	**Tissue is required**	Blood tests can suggest amyloidosis but cannot prove it. A biopsy is taken from an involved organ, from the marrow, or from the abdominal fat pad, which is a simple bedside sample.
2	**Congo red**	A stain that binds amyloid and turns it red or orange under ordinary light. Under polarized light the deposits glow apple green, a property called birefringence, and that glow is the confirmation.
3	**Typing is a separate step**	More than two dozen proteins can form amyloid. Immunostaining or mass spectrometry determines which one is present in your tissue, and this step is not optional.
4	**AL is not the only answer**	Transthyretin amyloid is common in older adults and is treated completely differently. A monoclonal protein in the blood plus amyloid in tissue does not automatically mean the two are related.

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Your report

How to read the document, and what to ask about it

WHAT YOU ARE LOOKING AT

Anatomy of a pathology report

1 The diagnosis line

The formal answer, written to be quoted. If you read one thing, read this.

2 Microscopic description

What was seen under the lens, including the percentage and how it was obtained.

3 Ancillary studies

Flow cytometry, immunohistochemistry, FISH and cytogenetics, each with its own result.

4 The comment

Where the pathologist reconciles findings that disagree and explains the reasoning.

5 Addenda

Results that arrived after the original report was signed, appended with their own dates.

6 The signature

A named physician who is accountable for the interpretation, and who can be contacted.

TAKE THESE WITH YOU

Questions worth considering

1. What was my plasma cell %, and did it come from the aspirate count or from the stained core biopsy?
2. Was my FISH performed on CD138 selected plasma cells, or on the sample as it arrived?
3. Which specific abnormalities were tested for, and which were found?
4. Am I being followed with MRD testing, and if so, at what sensitivity was my last result reported?
5. Was my diagnostic sample stored so that a sequencing based MRD fingerprint can be established?
6. May I have a copy of my full pathology report, including the addenda?

RESOURCES

Where to read more, without falling down a hole

MyPathologyReport.ca

A free, physician written site explaining pathology terms in plain language. Much of tonight's material comes from its guides, and I co-wrote the multiple myeloma one.

What to look up there

Multiple myeloma, plasma cell neoplasm, MGUS, plasmacytoma, amyloid, CD138, flow cytometry, FISH and bone marrow biopsy each have their own entry.

Your own report

The single most useful document you can study, because it is about you rather than about a population.

Your pathologist

Increasingly reachable. Some centers, including mine, now run clinics where patients meet the pathologist directly.

YOU ASKED FOR AN UPDATE

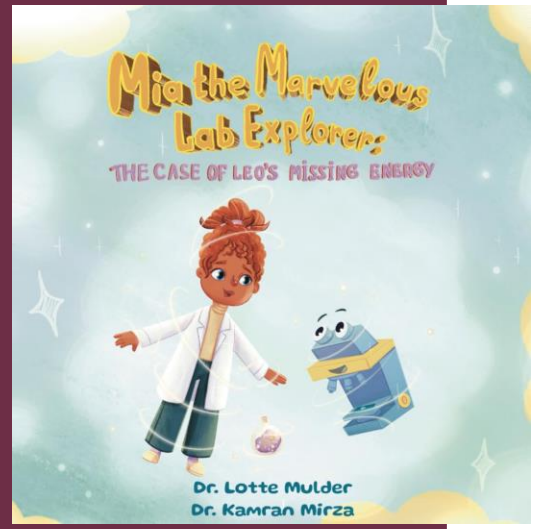
Mia the Marvelous Lab Explorer

The book

- Mia the Marvelous Lab Explorer: The Case of Leo's Missing Energy
- Written with Lotte Mulder for young readers, following a laboratory scientist solving a medical mystery
- Reviews have been kind, and the response from laboratory families has been the best part
- The MissionMarvelous campaign has raised thousands of dollars toward getting copies into classrooms

Why a children's book

Nobody grows up wanting to be a laboratory scientist, because nobody grows up knowing the job exists. The laboratory workforce shortage that affects your turnaround times begins with that invisibility, roughly two decades before it reaches your chart. A picture book is a slow instrument, and it is aimed at the right end of the problem. More books in the series are planned, funding permitting.



Three things to take with you

1. **Every number has a method behind it**
   Ask which method produced it, and small confusing differences stop being confusing

2. **Clonality is the whole game**
   One parent instead of many, whether measured by stain, by ratio or by sequence

3. **Negative always comes with a depth**
   Read the sensitivity attached to it, because that is the actual claim being made

Thank you. Questions, please.

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