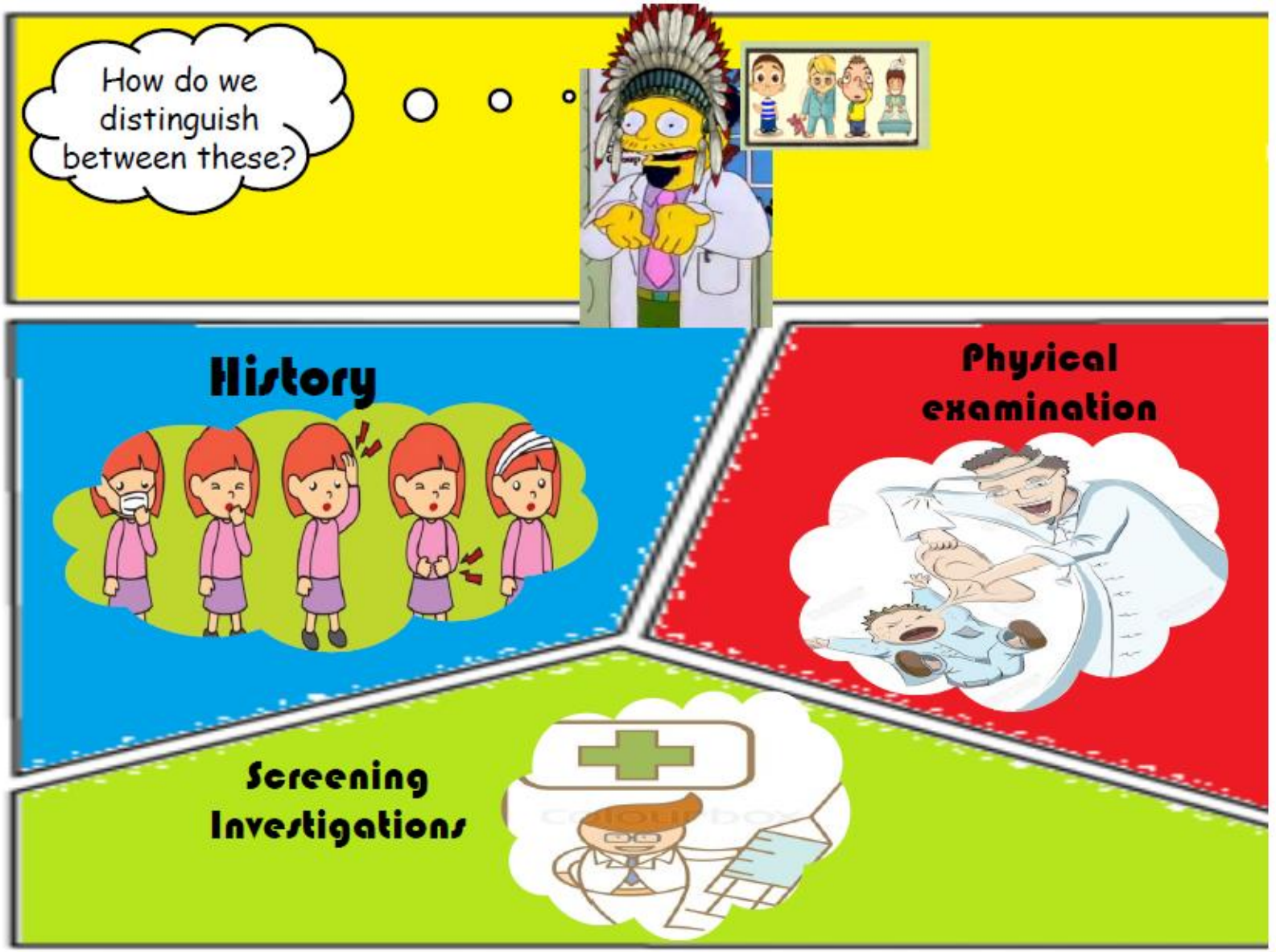
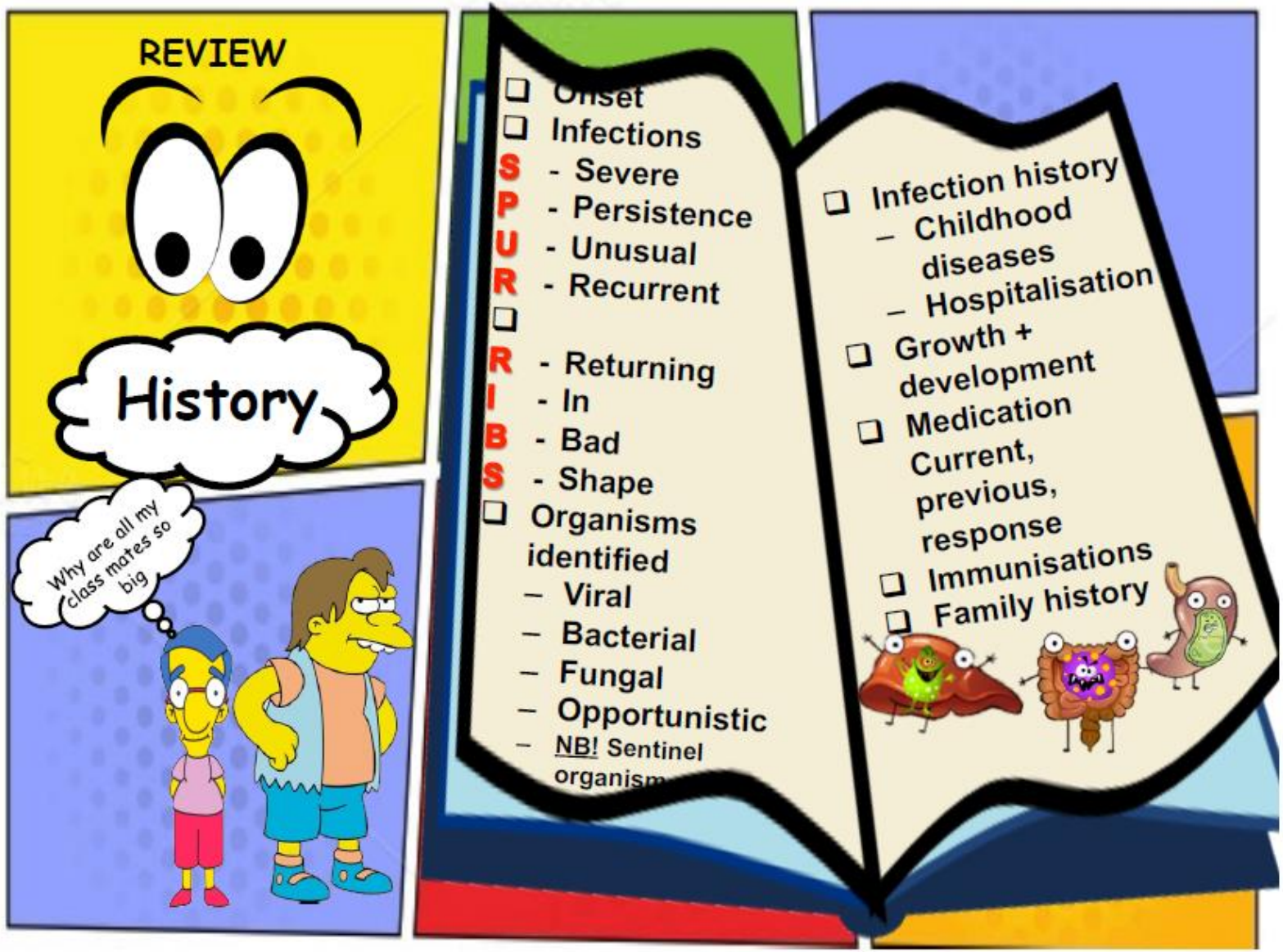

Jonny
Mom
When should I worry about recurrent / chronic airway infections?
When in doubt, order SPUR RIBS!
Infection
Pseudomonas Aeruginosa
Dr SPUR
UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA
AMPATH
Dr Cathy van Rooyen
AMPATH


In the
Spur
Steak Ranches
A taste for life
Good day Samson family
Jonny, would you like some of those SPUR Ribs you love?
Aargh, I feel sick. I can't possibly eat anything
This is the 10th time this year!
What! Too sick for Ribs? I suggest you make an appointment with Dr Spur
Mom calls immediately to make an appointment with Dr SPUR


At the Doctor's room
Good Day, I am Dr SPUR
Check History
Examine patient
Jonny has recurrent infections
Despite the best treatment, Jonny is
Returning
In
Bad
Shape ,,,
They seem to be ,,,,,
Severe
Persistent
Unusual
Recurrent
PID?
STOP
Whoa!..... not so fast
What else can it be?


I am "normal" (50%)
I am atopic (30%)
What else could it be?
I am chronically ill (10%)
I have a PID (10%)


How do we distinguish between these?
History
Physical examination
Screening Investigations


REVIEW
History
Why are all my class mates so big
Onset
Infections
S - Severe
P - Persistence
U - Unusual
R - Recurrent
R - Returning
I - In
B - Bad
S - Shape
Organisms identified
– Viral
– Bacterial
– Fungal
– Opportunistic
– NB! Sentinel organism
Infection history
– Childhood diseases
– Hospitalisation
Growth + development
Medication
Current, previous, response
Immunisations
Family history

FBC + diff:

- **Lymphocytes:**
  - Lymphopenia (age ranges)
  - Repeat - persistent (2°infection)
  - Lymphocyte count <1 x 10^9
  - Persistent lymphocytoses
- **Neutrophils:**
  - Neutropenia (1° or 2° immunodeficiencies)
  - Neutrophilia :
    - bacterial infection
    - Corticosteroids
    - LAD
- **Eosinophilia:**
  - Allergy
  - Some forms of PID
  - Parasitic infection
- **Platelets:**
  - Low/small : WAS
  - Increased: acute phase
- **RBC**
  - Anaemia – chronic disease
  - Auto-immune cytopenias

Allergy screen: (depending on history)

- Phadiatop + breakdown
- Food screen
- SPT
- IgE

Secondary causes/ chronic diseases:

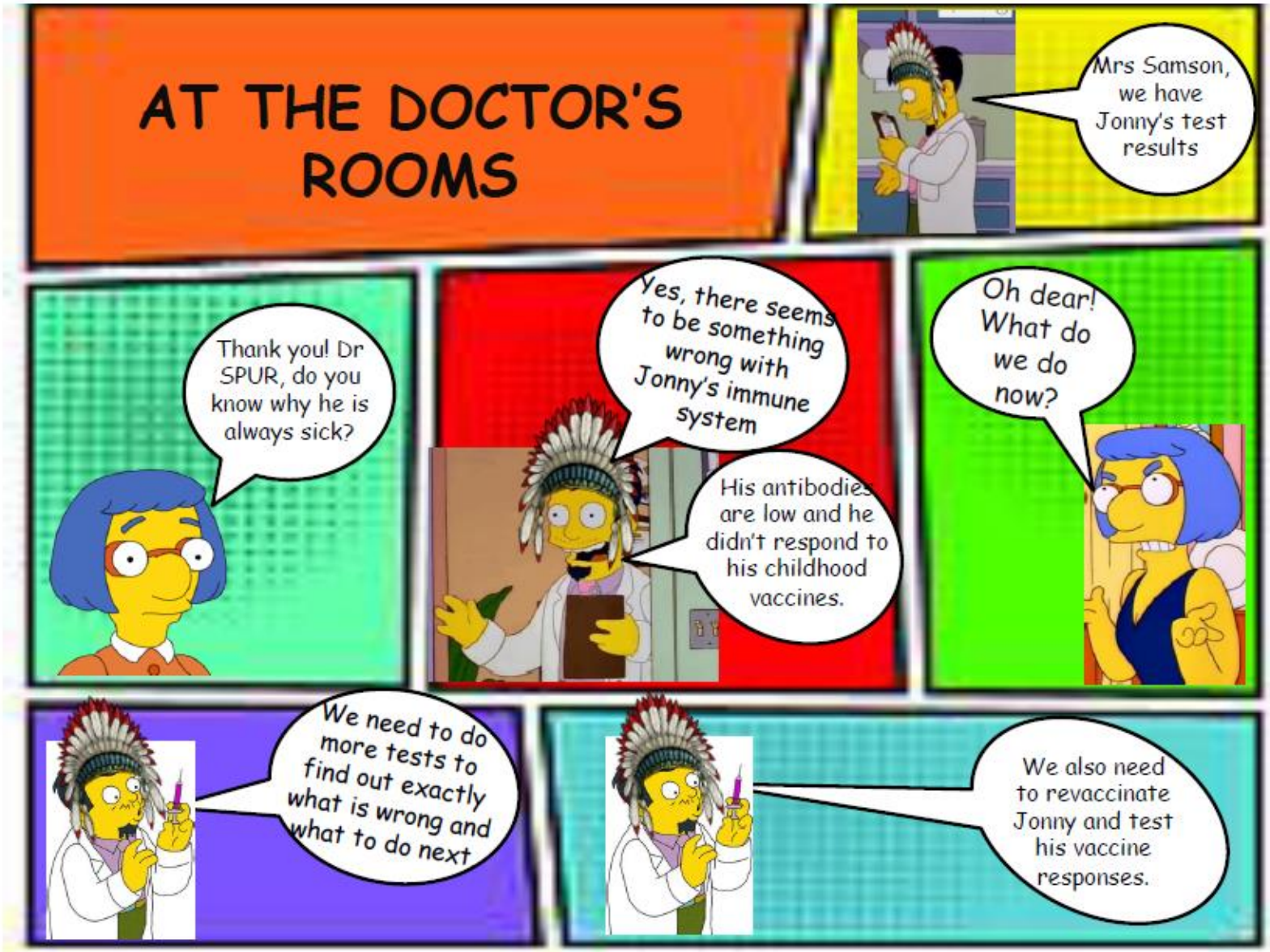
- HIV test
- Blood glucose
- Urinalysis: proteins
- Basic chemistry: urea , creatinine, albumin
- ESR/CRP: infections/ inflammatory disorders
- CF screening (sweat chloride test/genetic sequencing)

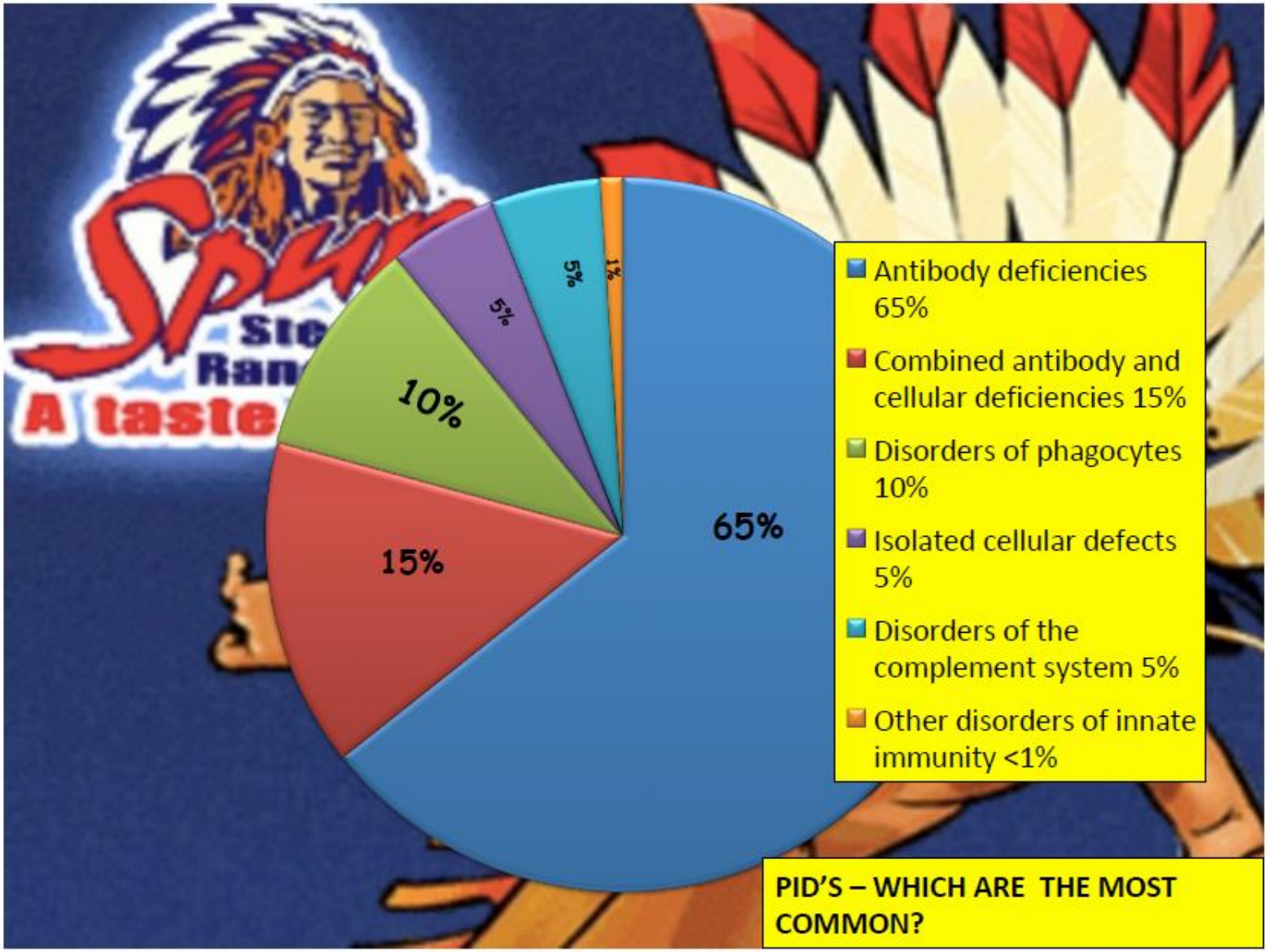
Lab investigations (based on clinical suspicion)

Basic Humoral Immune screen (65% of PID's):

- Ig G, A, M
- Antibodies to diptheria, tetanus, S.pneumoniae + H.influenzae

AT THE DOCTOR'S ROOMS




65%
15%
10%
5%
5%
1%
Antibody deficiencies 65%
Combined antibody and cellular deficiencies 15%
Disorders of phagocytes 10%
Isolated cellular defects 5%
Disorders of the complement system 5%
Other disorders of innate immunity <1%
PID'S – WHICH ARE THE MOST COMMON?

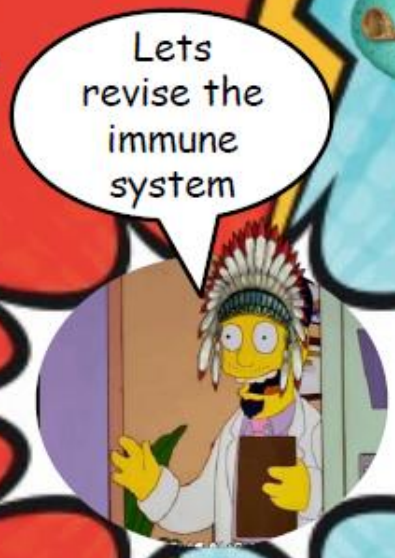
Adaptive Immune system

B-cells

- Humoral immunodeficiency
- Recurrent bacterial infections e.g. s pneumonia, h.influenzae, moraxella catarrhalis

T-cells

- Cellular or combined immunodeficiency
- predominantly viral + fungal infections



Innate Immune system

Neutrophils

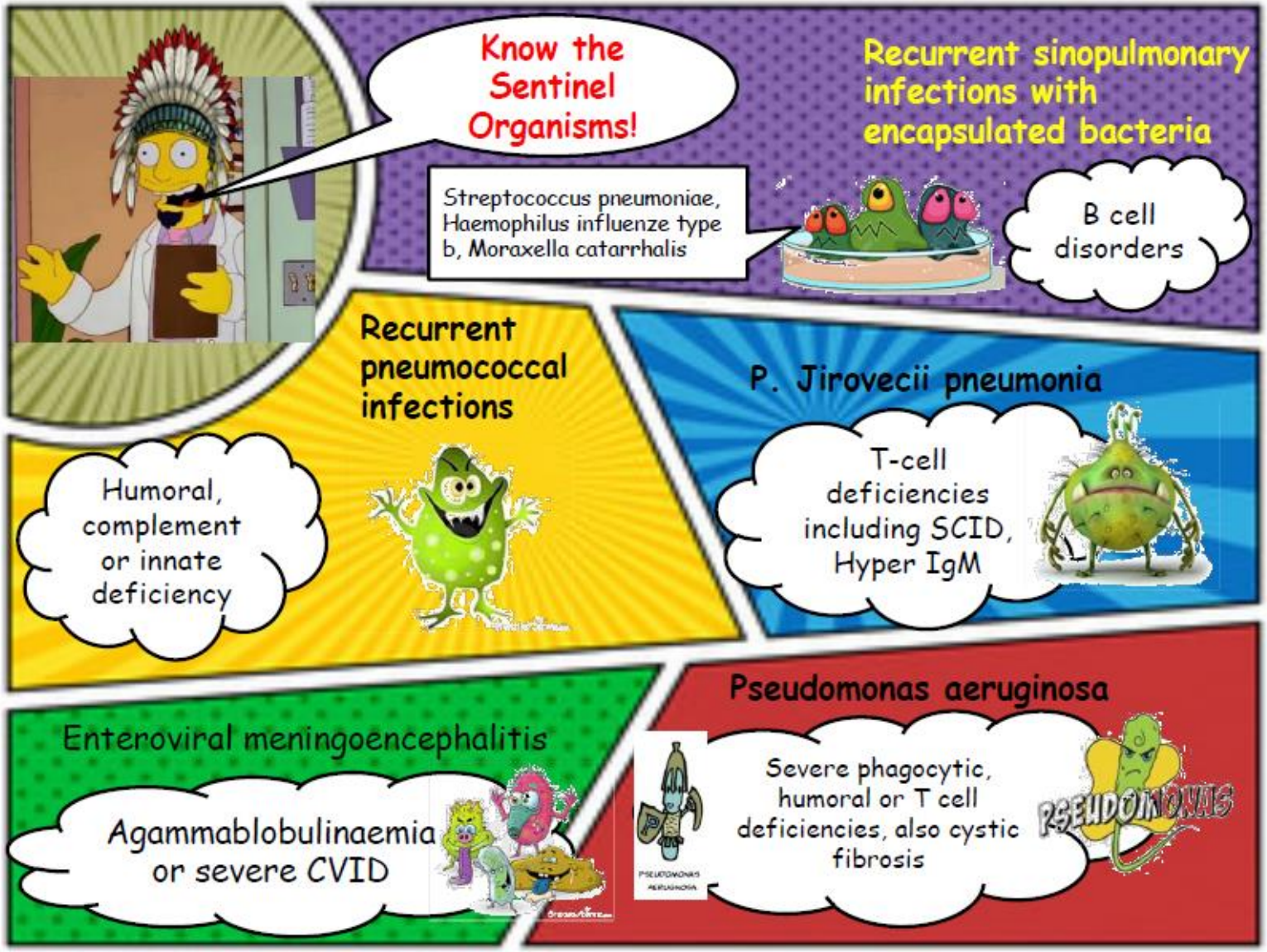
- S. aureus
- Fungal infection
- Other bacterial infections, e.g serratia, pseudomonas, etc

Complement

- Pyogenic infections
- Recurrent neisserial infections

NK-cells

- Herpes virus and papilloma-virus infections


Know the Sentinel Organisms!
Recurrent sinopulmonary infections with encapsulated bacteria
Streptococcus pneumoniae, Haemophilus influenze type b, Moraxella catarrhalis
B cell disorders
Recurrent pneumococcal infections
Humoral, complement or innate deficiency
P. Jirovecii pneumonia
T-cell deficiencies including SCID, Hyper IgM
Enteroviral meningoencephalitis
Agammablobulinaemia or severe CVID
Pseudomonas aeruginosa
Severe phagocytic, humoral or T cell deficiencies, also cystic fibrosis
PSEUDOMONAS

Recurrent infections with S.aureus, Coagulase Negative Staphylococci, Serratia marcescens or Aspergillus spp.

Phagocyte dysfunction

Recurrent herpes viral infections, including HSV, CMV and EBV

NK cell deficiencies and combined T cell defects including DOCK 8 deficiency

Know the Sentinel Organisms

Recurrent Staphylococcal skin infections, abscesses, lung cysts or pneumonia

- Hyper-IgE syndrome
- CGD

Infections with live vaccines (including BCG, oral polio vaccine, measles, varicella)

Severe primary immunodeficiencies, including SCID and XLA

Prolonged or recurrent Candida infections involving the mucous membranes

T cell immunodeficiency Immune dysregulation syndromes including APECED

Recurrent invasive Neisserial infections

Terminal complement deficiency

Know the Sentinel Organisms

Recurrent molluscum contagiosum and/ or persistent/ extensive/ recurrent warts

T cell defect, innate immune defect or combined defects e.g. WHIM syndrome

Systemic or deep infections with nontuberculous mycobacteria

Interferon gamma or Il-12 receptor deficiency SCID

Adaptive Immune system

B-cells

- Ig G, A,M
- IgG subfractions
- Vaccine responses: diptheria, tetanus, H.influenzae, S pneumoniae.
- B cell numbers
- Class-switched memory B-cells
- KRECS
- BTK, CD40, CD40L, etc.

T-cells

- Lymphopenia
- T-cell numbers: (CD 4 and CD 8 cells)
- Additional phenotyping:
  - RTE/Naïve/ memory T-cells
  - T cell receptor type
- TRECS
- T-cell proliferation to
  - Mitogens
  - Recall antigens

More specialised tests can be done, e.g. flow-cytometry/ genetic testing.

Innate Immune system

Phagocytes (Neutrophils)

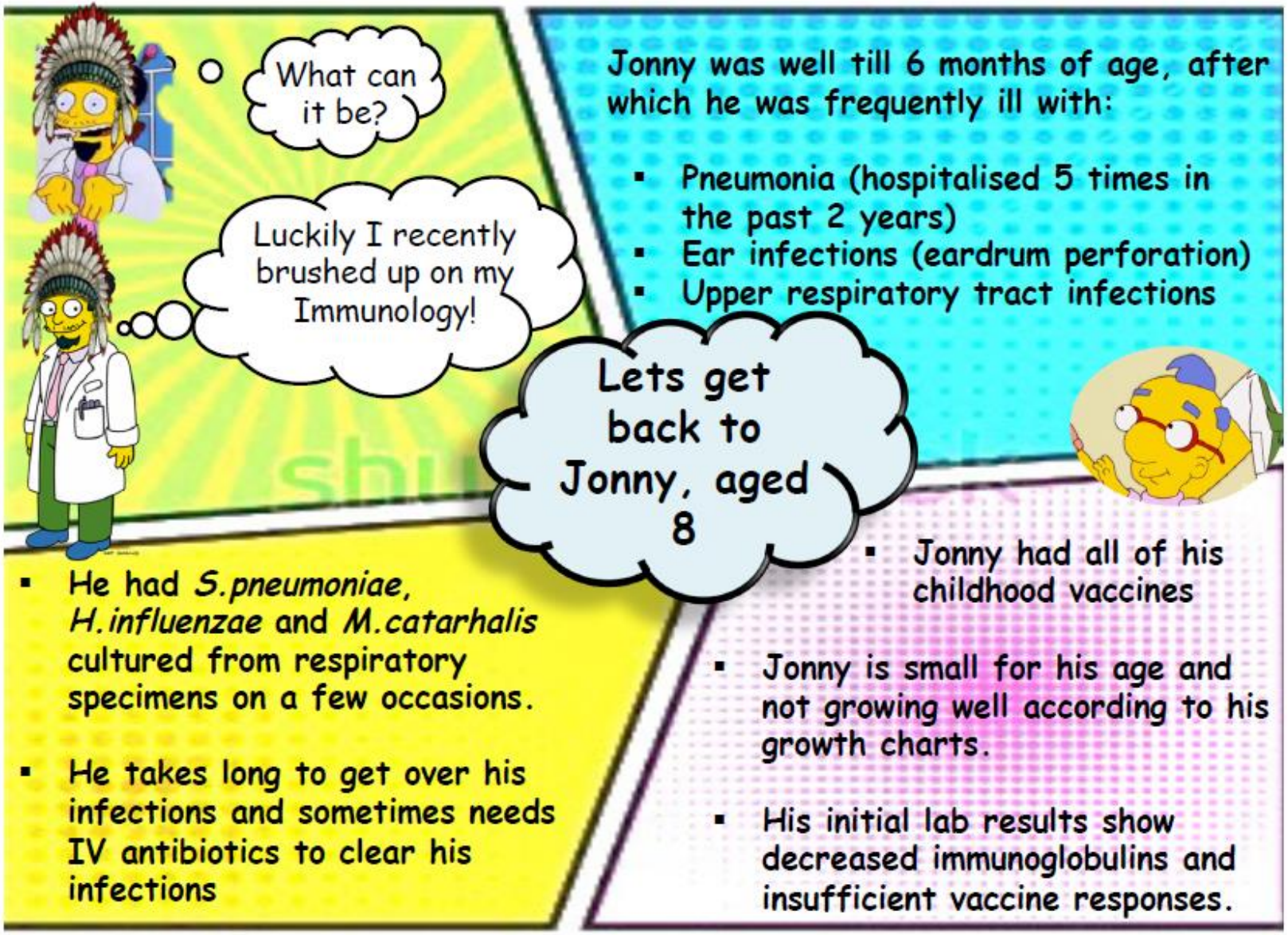
- FBC: neutrophil count
- Neutrophil functions:
  - Oxidative burst
  - Phogocytosis
  - Chemotaxis

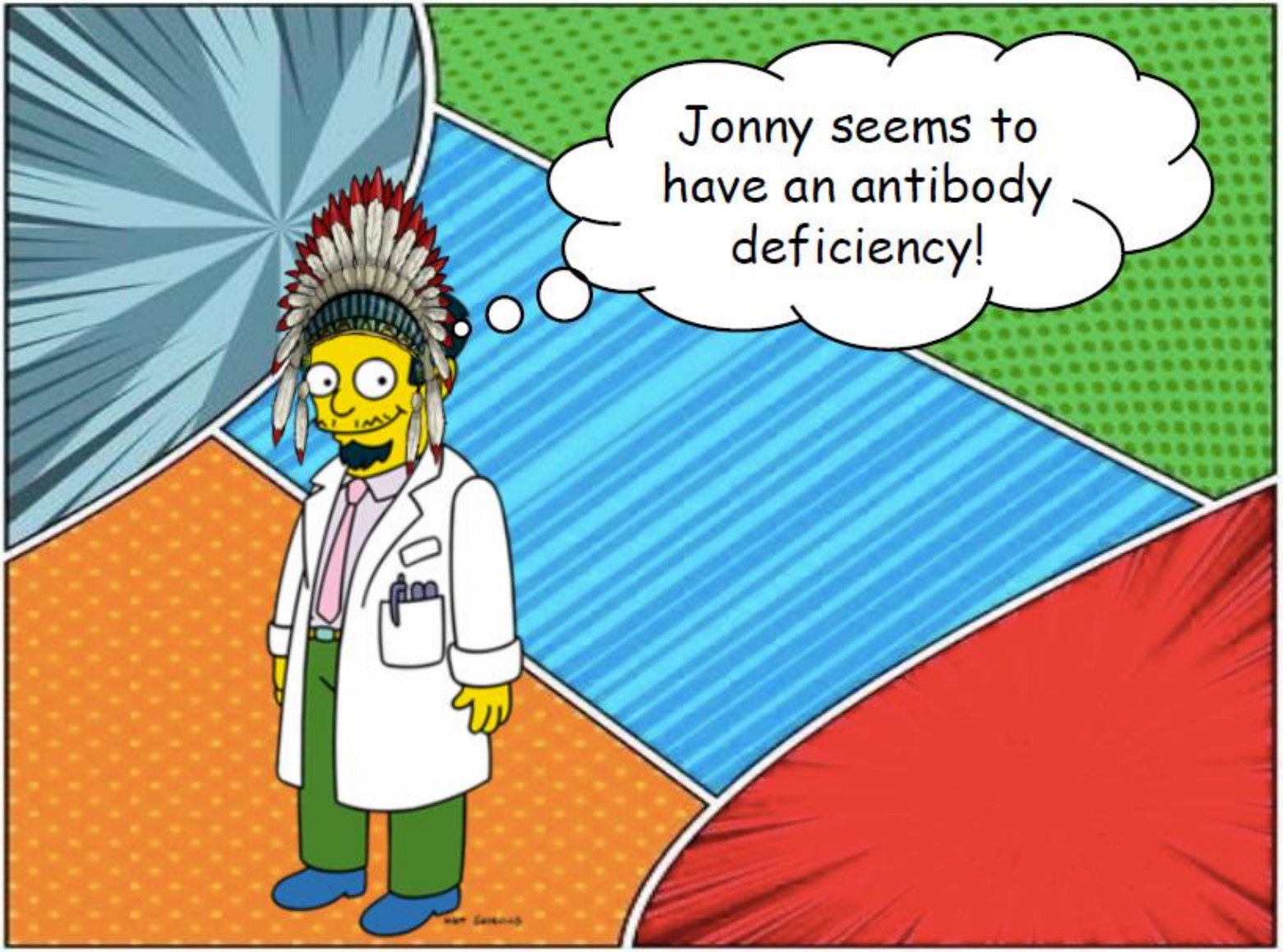
Complement

- Functional assays for classic + alternate pathways
- MBL
- Individual complement components

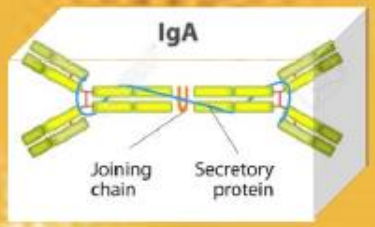
NK-cell deficiency

- NK numbers
- NK functions


What can it be?
Luckily I recently brushed up on my Immunology!
Jonny was well till 6 months of age, after which he was frequently ill with:
Pneumonia (hospitalised 5 times in the past 2 years)
Ear infections (eardrum perforation)
Upper respiratory tract infections
Lets get back to Jonny, aged 8
He had S.pneumoniae, H.influenzae and M.catarhalis cultured from respiratory specimens on a few occasions.
He takes long to get over his infections and sometimes needs IV antibiotics to clear his infections
Jonny had all of his childhood vaccines
Jonny is small for his age and not growing well according to his growth charts.
His initial lab results show decreased immunoglobulins and insufficient vaccine responses.

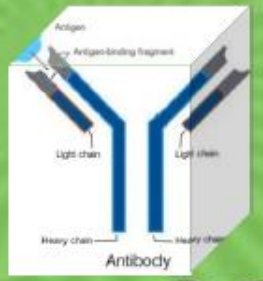

Jonny seems to have an antibody deficiency!

SELECTIVE IgA DEFICIENCY

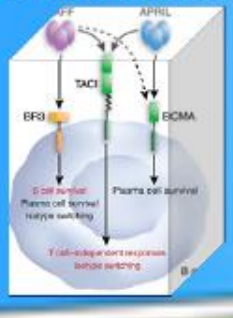


IgG SUBCLASS DEFICIENCY

SPECIFIC ANTIBODY DEFICIENCY

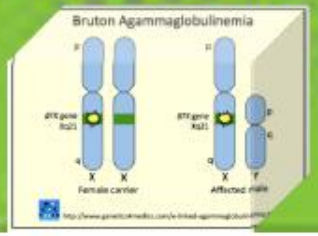


COMMON VARIABLE IMMUNODEFICIENCY (CVID)

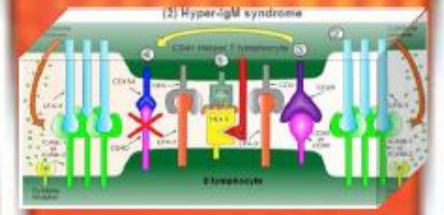


Look what I learned about types of antibody deficiency

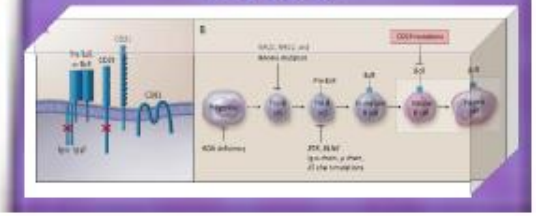
X-LINKED AGAMMAGLOBULINEMIA (XLA)



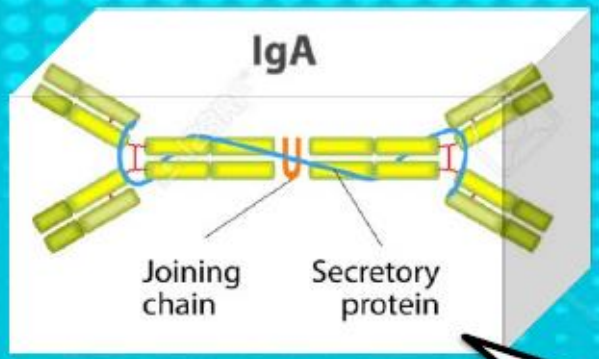
HYPER IgM SYNDROME (HIGM)



TRANSIENT HYPOGAMMA-GLOBULINAEMIA OF INFANCY



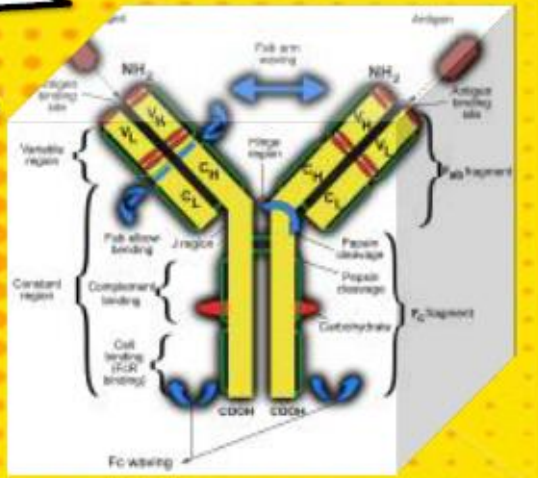
SELECTIVE IgA DEFICIENCY



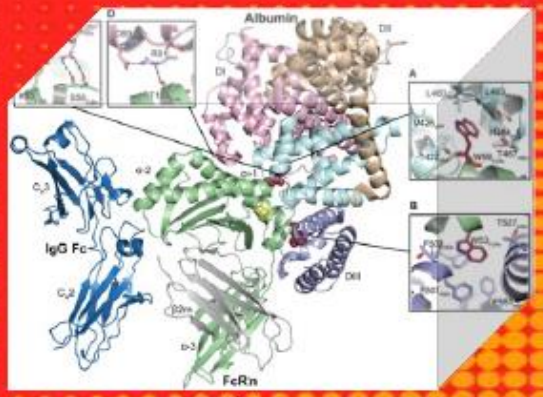
What antibody deficiencies are we looking for?

IgA deficiency

- Range from asymptomatic to severe
- Often associated:
  - IgG subclass deficiency
  - Specific ab deficiency
  - Atopy
  - CD and autoimmunity



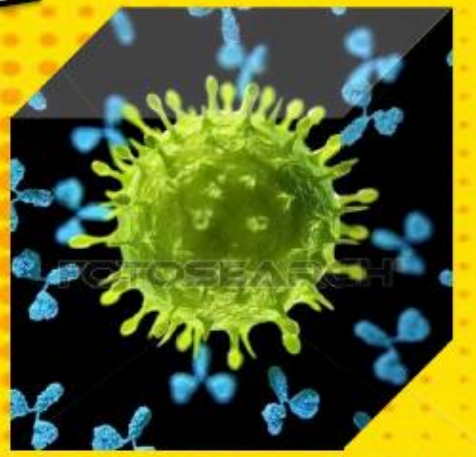
IgG SUBCLASS DEFICIENCY



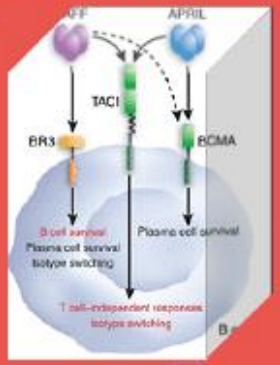
What antibody deficiencies are we looking for?

IgG subclass deficiency

- Normal total IgG
- IgG2 may be associated with ↓ polysaccharide response
- ↓ antibodies to S.pneumoniae and H.influenzae



COMMON VARIABLE IMMUNODEFICIENCY (CVID)



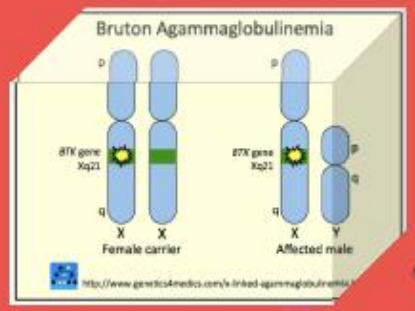
CVID

- ↓ IgG, IgA and IgM often ↓
- Vaccine responses impaired.
- May have a slight T-cell defect, autoimmunity
- Recurrent infections with encapsulated organisms

What antibody deficiencies are we looking for?

- Unusual infections e.g. campylobacter, mycoplasma arthritis, persistent Giardia
- Patients often have low class-switched memory B-cells.
- Complications like bronchiectasis, enteropathy, granulomatous disease, lymphoproliferate disease

X-LINKED AGAMMAGLOBULINEMIA (XLA)



XLA

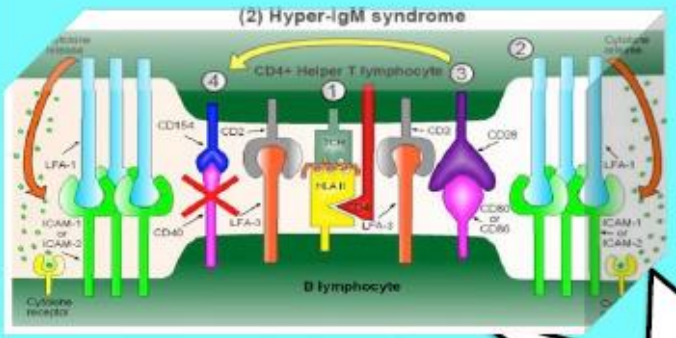
- B cells absent/ low
- IgA, M, G absent/ low
- Hypoplastic tonsils/ lymphoid tissue
- Btk protein absent (flow-cytometry) or mutated (genetic testing)
- No KRECS

What antibody deficiencies are we looking for?

Infections associated with XLA:

- URTI and LRTI with encapsulated organisms
- Staphylococcal septic arthritis
- Giardia, Salmonella and Campylobacter infections of the gut.
- Chronic enteroviral meningo-encephalitis

HYPER IgM SYNDROME (HIGM)



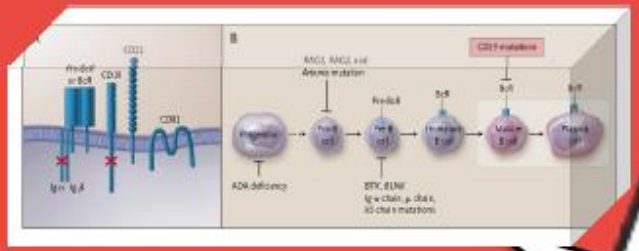
What antibody deficiencies are we looking for?

Hyper IgM syndrome

- Low IgG and IgA, high or normal IgM
- CD40L expression on T-cells may be abnormal (most common, X-linked)
- CD 40 expression on B-cells may be abnormal.

- Different types of hyper IgM syndrome. 5 currently identified. Additional genetic testing for AR forms
- Infections:
  - Recurrent URTI, LRTI
  - Additional risk for PJP and cryptosporidium infection.

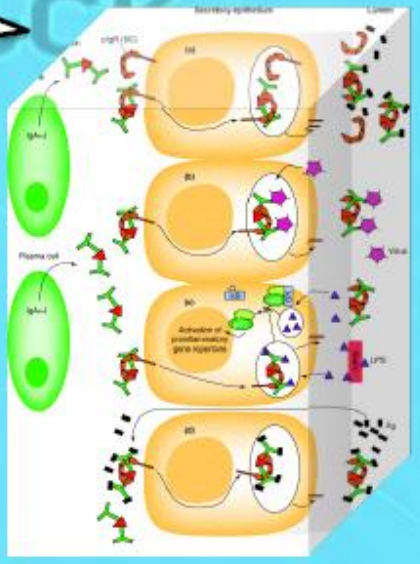
TRANSIENT HYPOGAMMA-GLOBULINAEMIA OF INFANCY

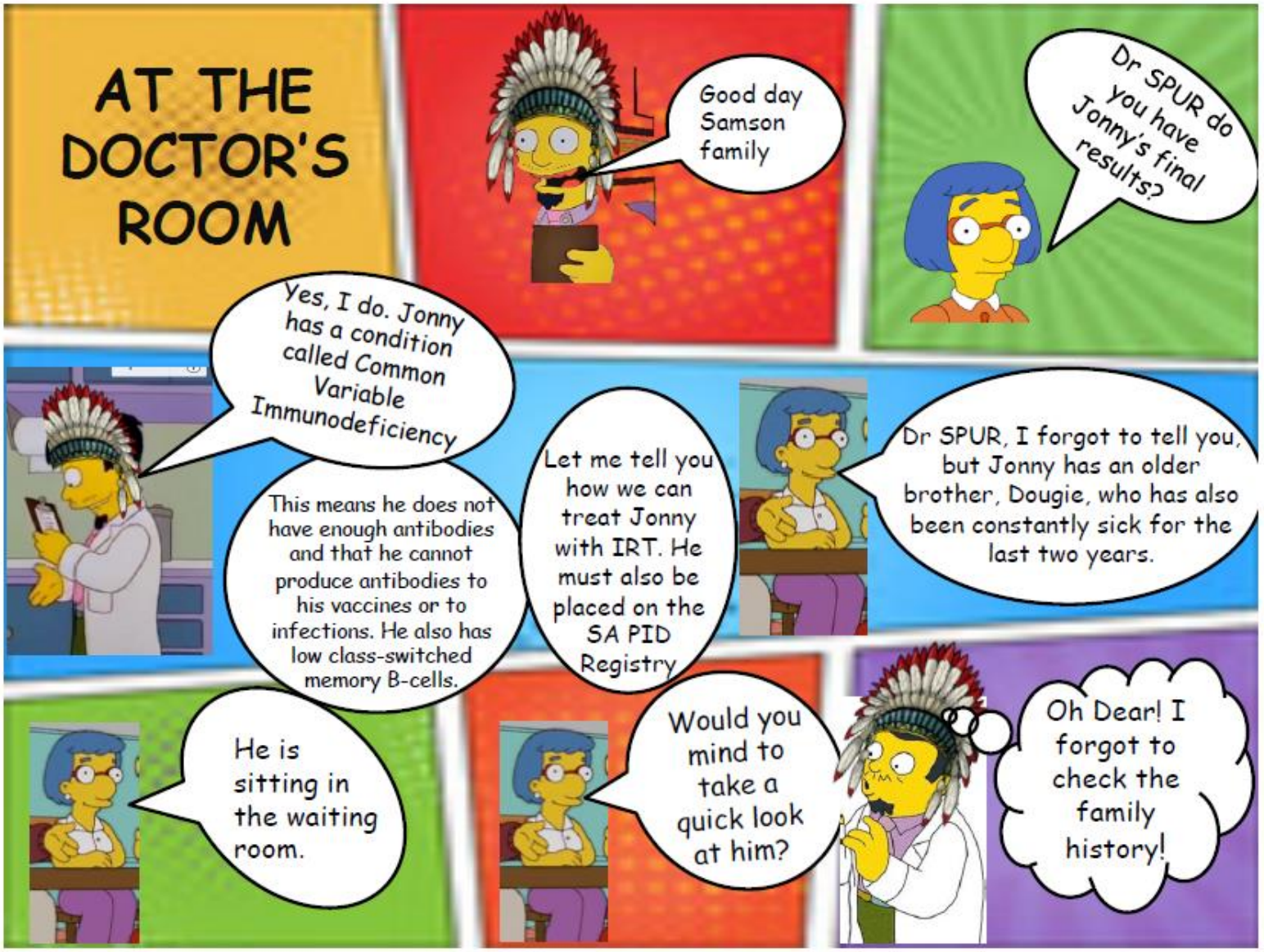


Transient hypogammaglobulinaemia of infancy.

- IgA and IgG decreased
- IgM mostly normal
- Must normalise by age of 4 years

What antibody deficiencies are we looking for?




AT THE DOCTOR'S ROOM
Good day Samson family
Dr SPUR do you have Jonny's final results?
Yes, I do. Jonny has a condition called Common Variable Immunodeficiency
This means he does not have enough antibodies and that he cannot produce antibodies to his vaccines or to infections. He also has low class-switched memory B-cells.
Let me tell you how we can treat Jonny with IRT. He must also be placed on the SA PID Registry
Dr SPUR, I forgot to tell you, but Jonny has an older brother, Dougie, who has also been constantly sick for the last two years.
He is sitting in the waiting room.
Would you mind to take a quick look at him?
Oh Dear! I forgot to check the family history!

Immune deficiency request form

SPUR

RIBS

IMMUNE DEFICIENCY REQUEST FORM

ANTIBODY (HUMORAL) DEFECTS

☐	Full Blood Count + Diff	FBC
☐	IgG, IgA, IgM	IMM
☐	IgE	IGE
☐	IgG subclasses	SUBG
++ ☐	Secretory IgA	SECA
☐	Lymphocyte subsets (B cell numbers)	IMMDEF
☐	S.pneumonia antibodies	SPAB
☐	H.influenzae antibodies	HINF
☐	Tetanus antibodies	TET
☐	Diphtheria antibodies	DIP
⊗ ☐	B-cell function	BF
† ☐	Memory B cells	BMEM
☐	Brutons Tyrosine Kinase	BTK
⊗ ☐	CD 40 Ligand	CD40L
⊗ ☐	TH 17 Cells	TH17

T-CELL DEFECTS

☐	HIV Antibodies (Screen)	HIV
☐	HIV PCR	HIVPCR
☐	Full Blood Count + Diff	FBC
☐	Lymphocyte subsets (T cell numbers)	IMMDEF
† ☐	Naive and memory Cells CD4	NAIVE4
† ☐	Naive and memory Cells CD8	NAIVE8
† ☐	Alpha beta/ gamma delta T cells	TCELLR
☐	Common Gamma Chain	DIVFL
	(put Common Gamma Chain in the comment field)	
○	***Lymphocyte proliferation tests to mitogens***	
☐	PHA	PHAPR
☐	PMA	PMARD
☐	PMA + ionophore	PMAIPR
☐	CD3	ACD3PR
☐	CD3 + IL-2	IL2PR
☐	CONA	CONPR
☐	PWM	PRMR
○	***Lymphocyte proliferation tests to recall antigens***	
☐	Varicella zoster	VZVPR
☐	Candida	CANPR
☐	Tetanus (put Tetanus in comment field)	DIVW

NEUTROPHIL DEFECTS

☐	Full Blood Count + Diff	FBC
⊗ ☐	Neutrophil functions	NEUTF
	(Neutrophil & Monocyte Oxidative burst, Phagocytosis & Chemotaxis)	
☐	Oxidative burst	BURST
☐	Phagocytosis	PHAGO
☐	Chemotaxis	MIGRA
☐	Leukocyte adhesion studies CD 11 & CD 18	LAD
∞ ☐	Neutrophil antibodies	DIVFL
	(Put neutrophil antibodies in comment field)	

COMPLEMENT DEFECTS

✳ ☐	Classic & Alternative pathways	HCOMP
☐	Complement 3 levels	C3
☐	Complement 4 levels	C4
✳ ☐	Mannan Binding Lectin	MBL

NATURAL KILLER CELL DEFECTS

☐	Lymphocyte subsets (NK cell numbers)	IMMDEF
⊗ ☐	NK cell function	NKF

NEWBORN SCREENING FOR SEVERE IMMUNODEFICIENCIES

† ☐	TREC & KREC Qualitative PCR	TRECPCR

ADDITIONAL GENETIC TESTING

++ ☐	DNA Isolation	PDNAPCR

CLINICAL DATA

Please provide a short Clinical History

SPECIAL INSTRUCTION

++ Saliva in sterile bottle.

⊗ Heparin tube. Kept at room temperature, must be <= 24hrs old. Blood samples drawn SUNDAYS to THURSDAYS. Always Stat. A normal adult control specimen must be sent with each patient, with the same R# as the patient, clearly marked "control".

† EDTA (E02) specimens. Kept at room temperature, must be <= 48hrs old. Blood samples drawn SUNDAYS to THURSDAYS. Always Stat. A normal adult control specimen must be sent with each patient, with the same R# as the patient, clearly marked "control".

○ 4-8 Citrate tubes depending on amount of tests- contact lab. (3-4 Citrate tubes for small baby/child). Kept at room temperature, must be <= 24hrs old. Blood samples drawn SUNDAYS to THURSDAYS. Always Stat. DO NOT CENTRIFUGE the tubes.

✳ SST tube. Directly after SST tube is drawn, the tubes must be put on COLD ice pack (NOT FROZEN) TO CLOT. Separate and SEND ON ICE.

∞ SST tube

† Dried blood spot or EDTA blood. Fill minimum two FULL circles on DBS.

++ EDTA tube of patient and both parents. Clearly label each with their names. Must be accompanied with genetic consent form.

Please phone Drs Sylvia van den Berg or Cathy van Rooyen for any queries on: (012) 678-0613/6/7

AMPATH