Approach to the genetic evaluation of a neonate

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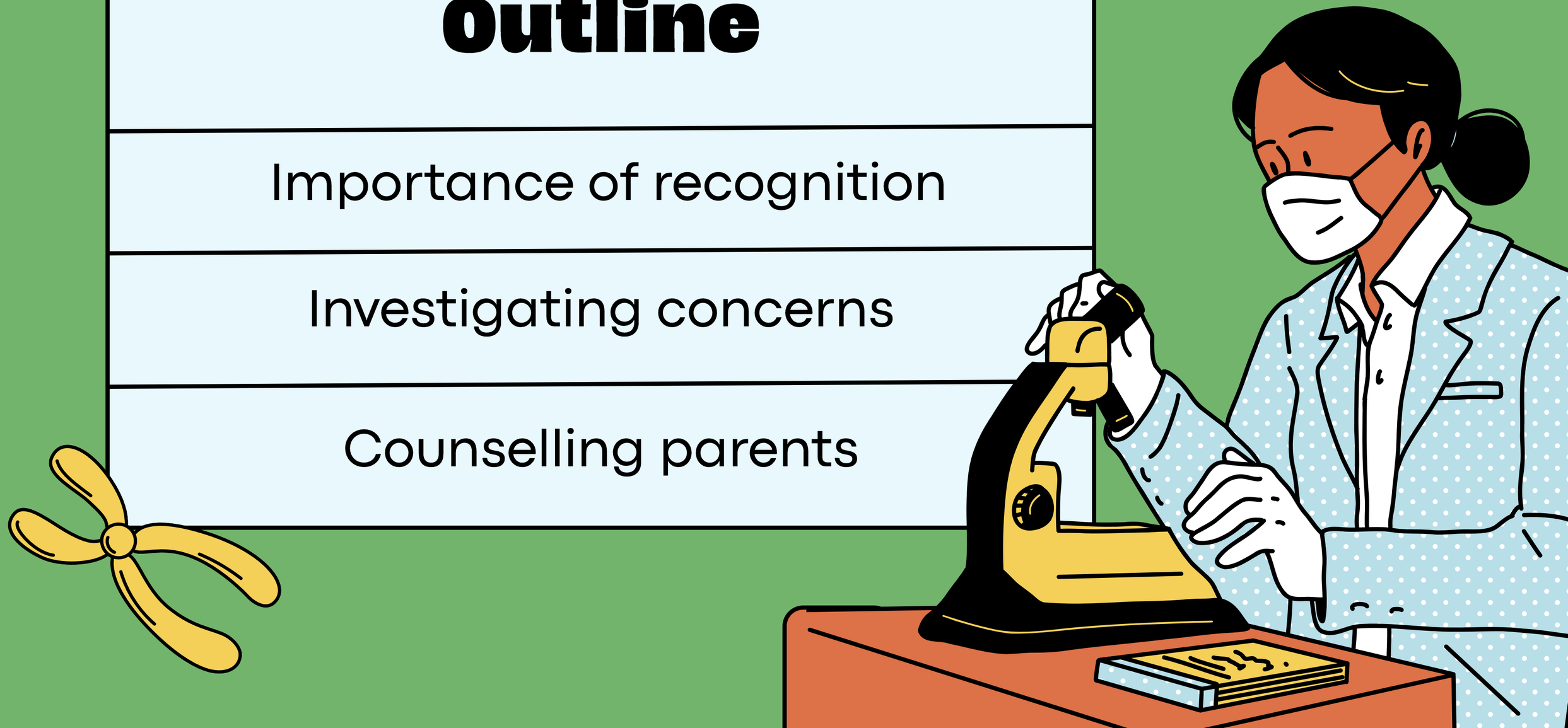
Outline

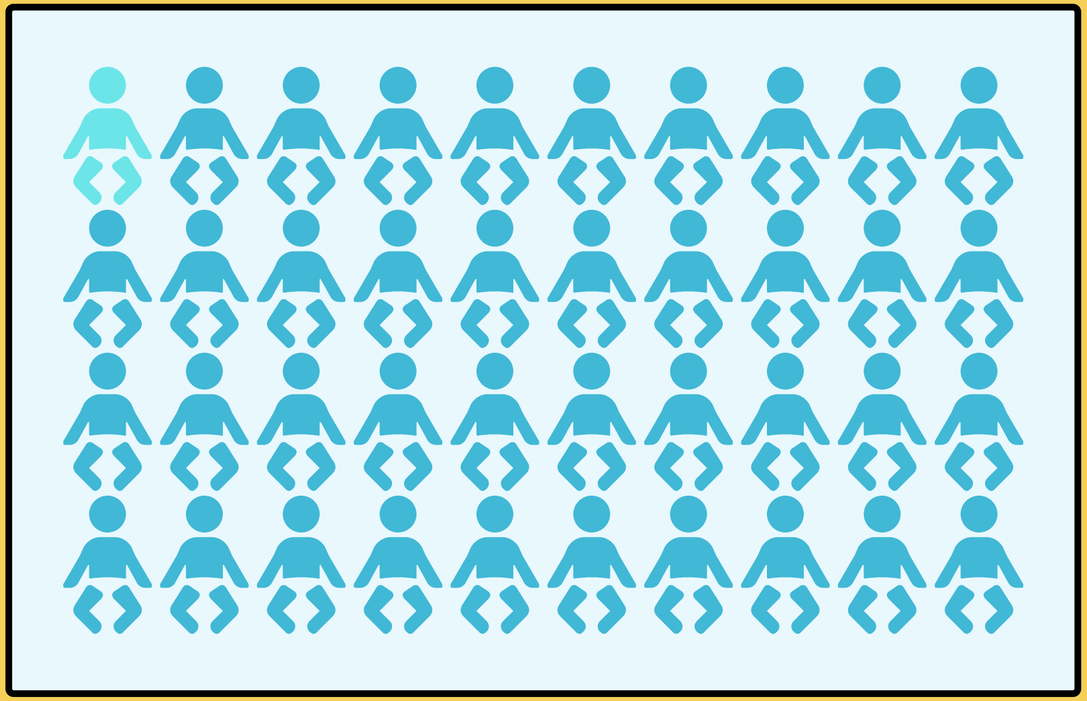
Importance of recognition

Investigating concerns

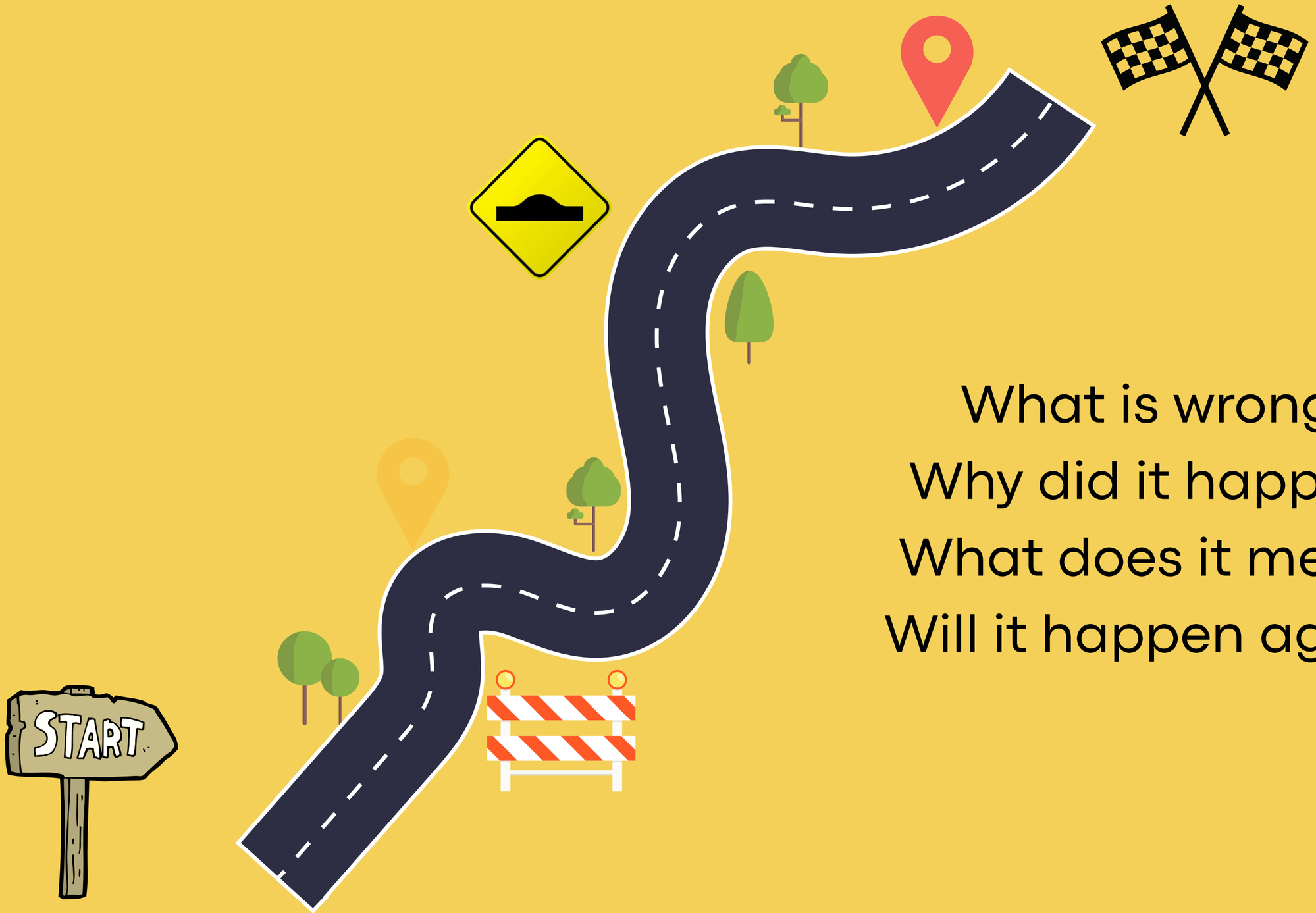
Counselling parents



Why are genetic conditions important?



Congenital disorder: Any abnormality affecting body structure or function that is present from birth



What is wrong?

Why did it happen?

What does it mean?

Will it happen again?

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slido.com

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What information do you want from the family history?

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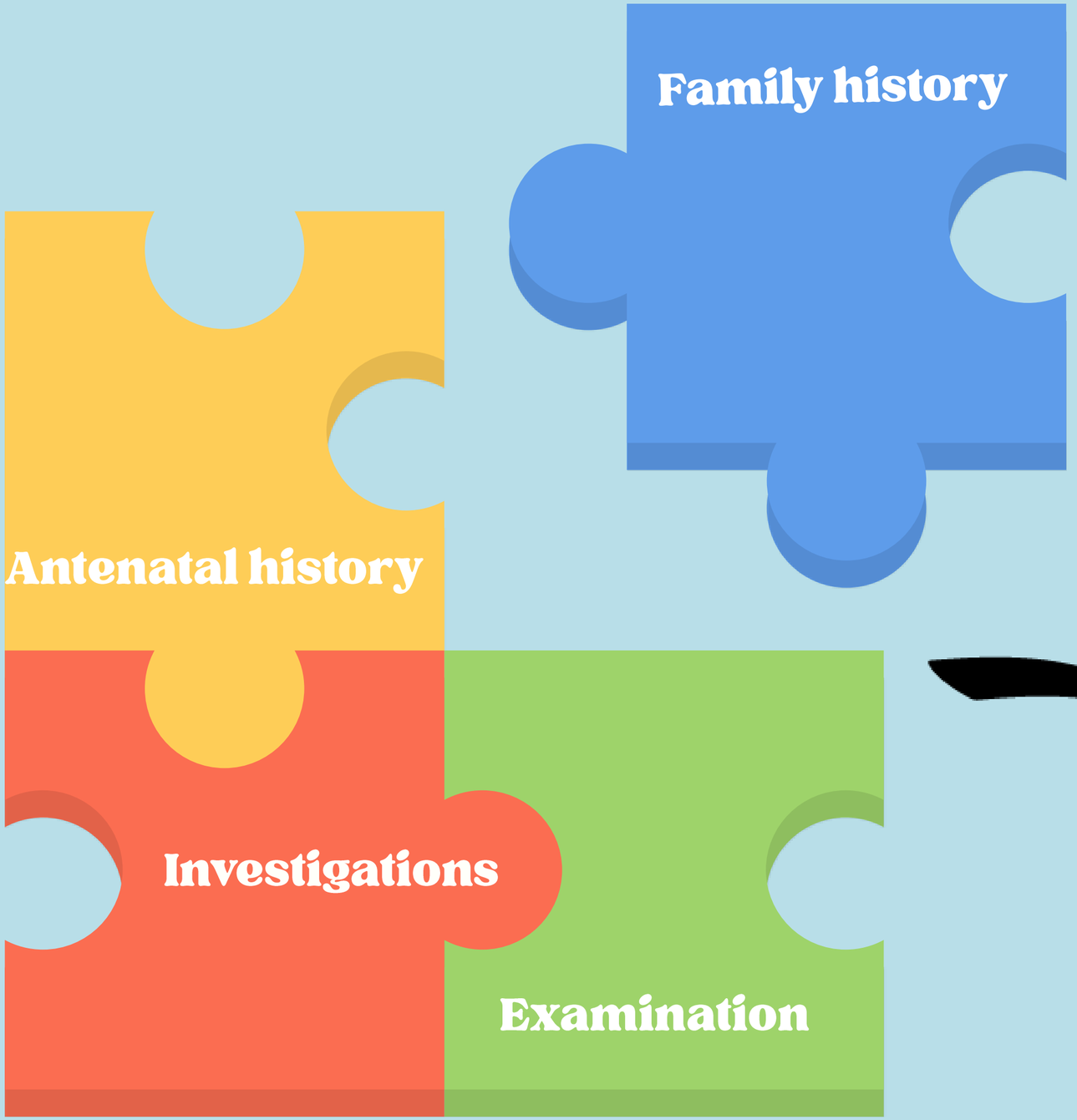
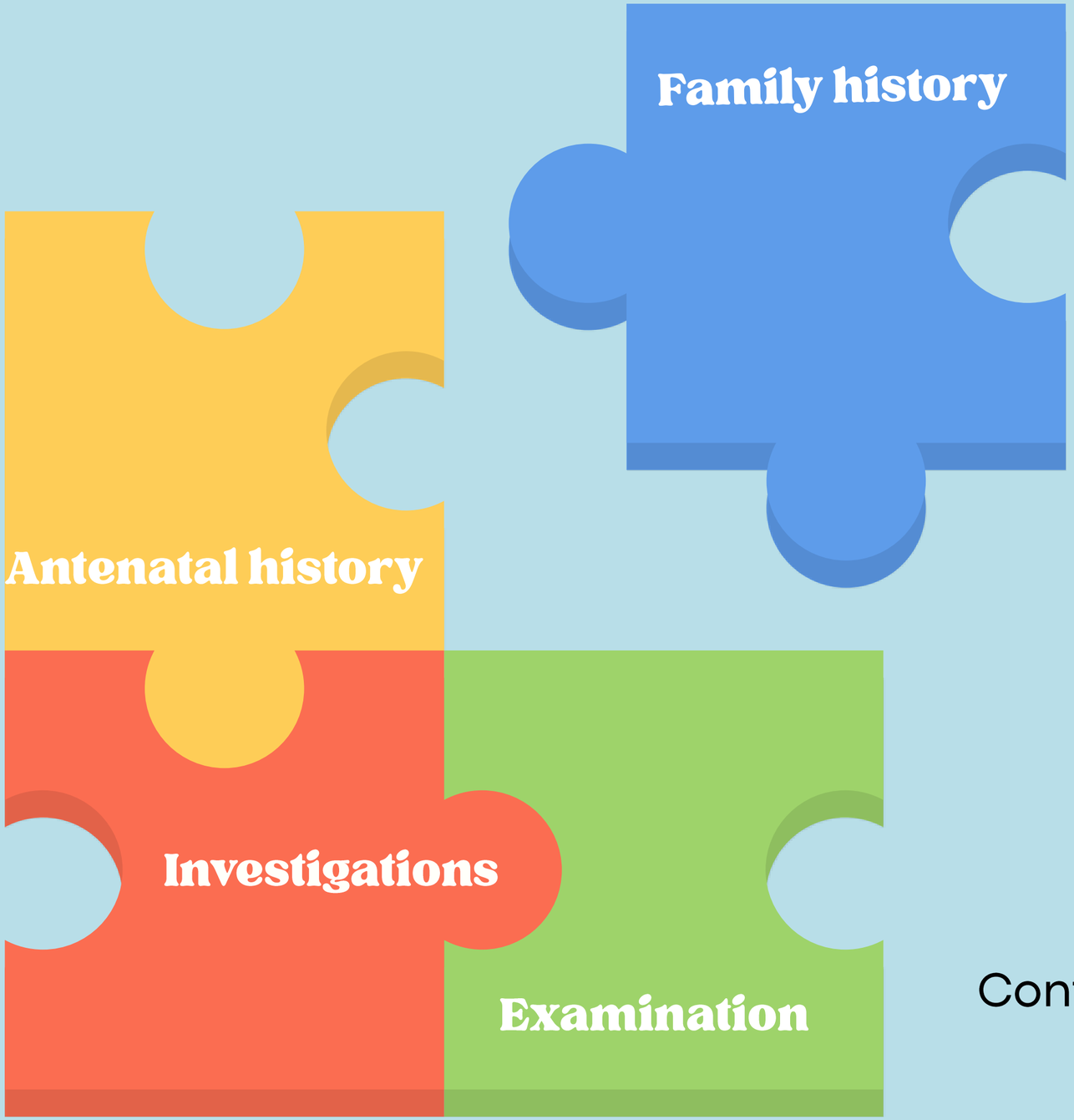
APPROACH TO THE EXAMINATION



Clinical diagnosis

APPROACH TO THE EXAMINATION



Clinical diagnosis

- Diagnosis by approximation
- Clinical diagnosis
- Syndromic search

Confirmatory investigations and testing
Hopefully (ideally) genetic

SCENARIO 1

History:
Mom's sister had isolated cleft lip
Well grown
No other structural abnormalities
Good suck

SCENARIO 2

History:
42 year old mom
Overlapping fingers
Clubfeet
IUGR
Cardiac murmur
Poor suck
Hypotonia

SCENARIO 3

History:
20 year old well mom
Normal growth parameters
Cardiac murmur
Prominent finger pads
Facial dysmorphism

Mechanism of congenital disorders

Malformation	A primary structural defect of an organ, or part of an organ that results from an inherent abnormality of development
Deformation	Defect that arises from an abnormal mechanical force that distorts an otherwise normal structure
Disruption	Abnormal structure of an organ or tissue as a result of external factors disturbing the normal developmental process.
Dysplasia	An abnormal organisation of cells into tissue

Mechanism of congenital disorders

Malformation	Chromosomal, single gene, multifactorial, teratogens
Deformation	Uterine constraint, oligohydramnios, twins
Disruption	Teratogen, vascular, ischaemia, infection
Dysplasia	Single gene

MAJOR ANOMALIES

Cardiac lesions
Microcephaly
Renal abnormality
Absent radius

MINOR ANOMALIES

Epicanthic folds
Postaxial polydactyly
Low set ears

Syndrome
recognisable pattern of symptoms, signs and dysmorphic features due to known or strongly suspected genetic cause
eg. Down syndrome caused by trisomy 21

Sequence
pattern of abnormalities resulting from a cascade of events started by a malformation
eg. Potter sequence resulting from renal agenesis

Association
collection of major malformations that occur more often than expected by chance and cannot be recognised as a syndrome or sequence
eg. VACTERL association

Significance of minor abnormalities

Single minor anomaly	15% of all newborns 3% have ass major anomaly
2 of more minor anomalies	0.8% of all newborns 11% have ass major anomaly
3 or more minor anomalies	0.5% of all newborns 90% have ass major anomaly
External minor anomalies of head & neck and hand	Constitutes 71% of all minor anomalies

Dysmorphic neonate: an approach to diagnosis in the current era. Tewari et al. 2016. Pediatric Dimensions

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What is the underlying etiology?

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SCENARIO 1

What is it?

Isolated cleft lip
Malformation

Why did it happen?

Likely multifactorial

What does it mean?

Feeding difficulties
Surgery
Speech or ENT concerns

Will it happen again?

Empiric recurrence risk
Some evidence for folate use

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History:
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Prominent fingerpads
Facial dysmorphism

SCENARIO 2

What is it?

Associated / syndromic cleft

Why did it happen?

Chromosomal

What does it mean?

LIKELY (but not definitely) : Additional neurological concerns
Shortened life span

Will it happen again?

Depends on the result: non disjunction (more common) vs translocation (rare)

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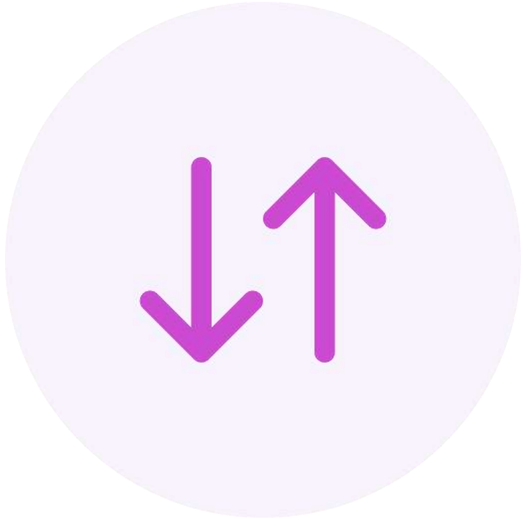

Rank the order genetic investigation would you do?

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SCENARIO 3

What is it?

Associated / syndromic cleft

Why did it happen?

Chromosomal
Single gene

What does it mean?

Uncertain...
Need more information
Prognosis based on "sum of things"

Will it happen again?

uncertain

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Do you proceed with genetic testing?

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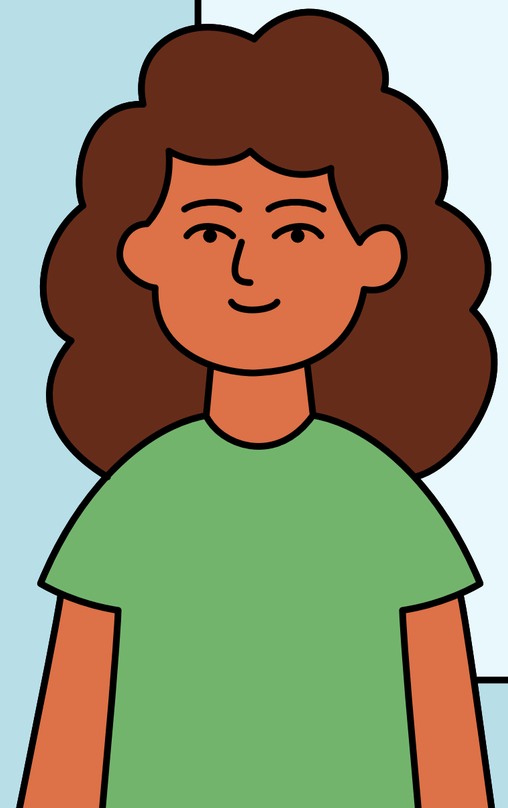
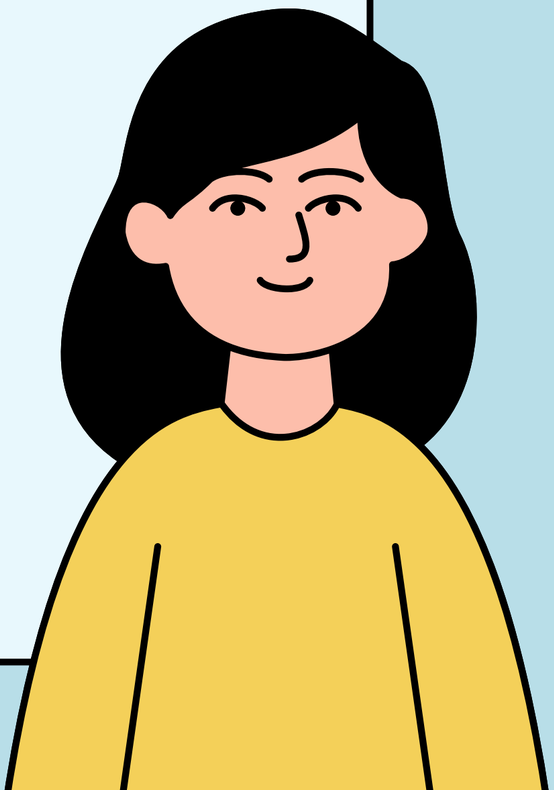
Special investigations

Nuclear DNA and mitochondrial DNA

Nuclear DNA
Chromosomal changes
Smaller copy number changes

Single gene:
Sequencing change
Base pair deletion or duplication
Triplet repeat
Methylation changes



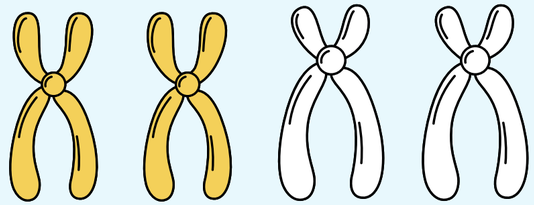


Special investigations

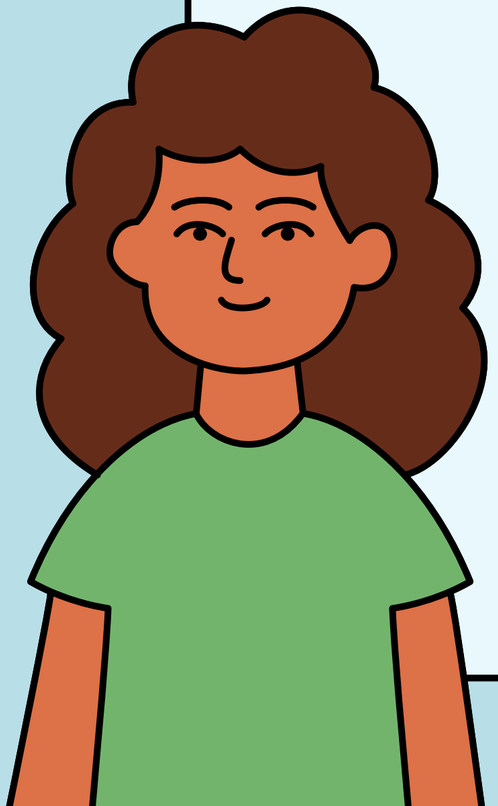
Nuclear DNA:

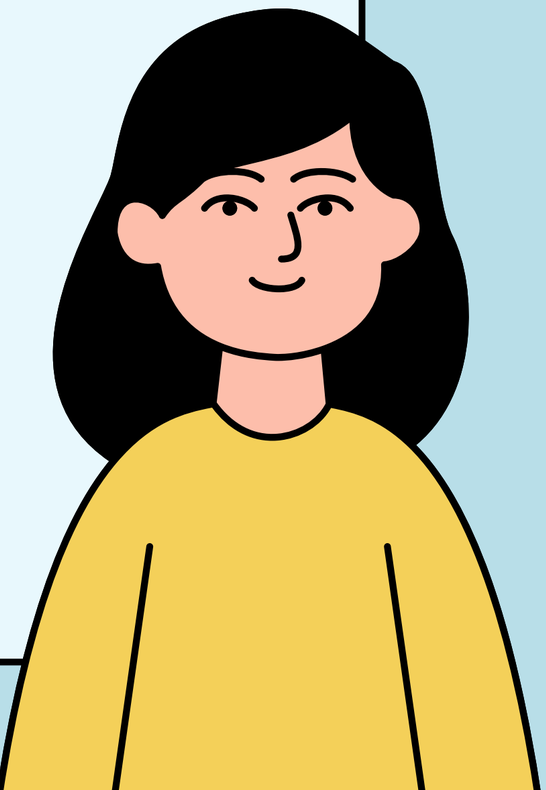
Chromosomal changes

Smaller copy number changes



chr 18 chr 21





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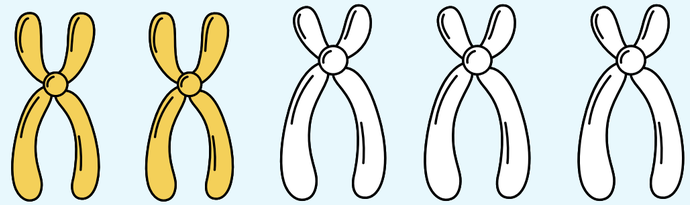

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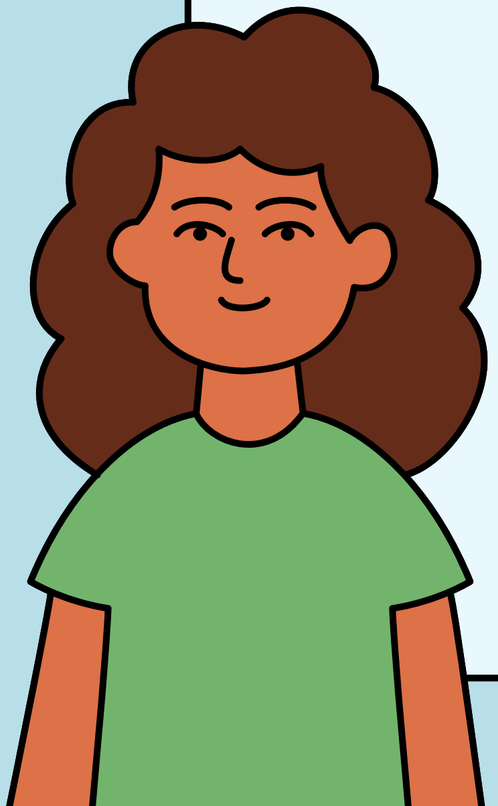

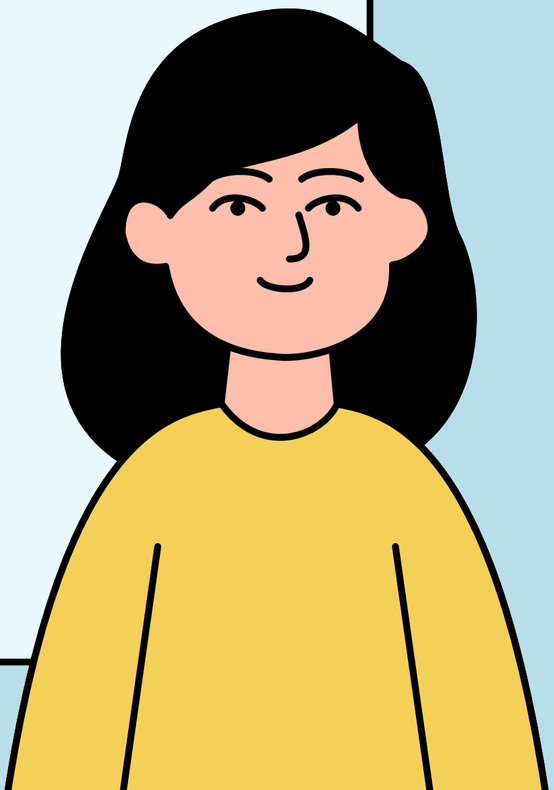

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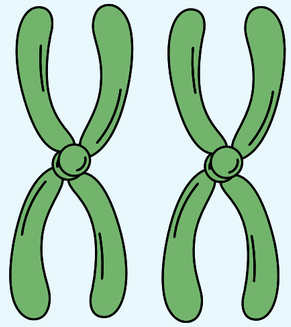

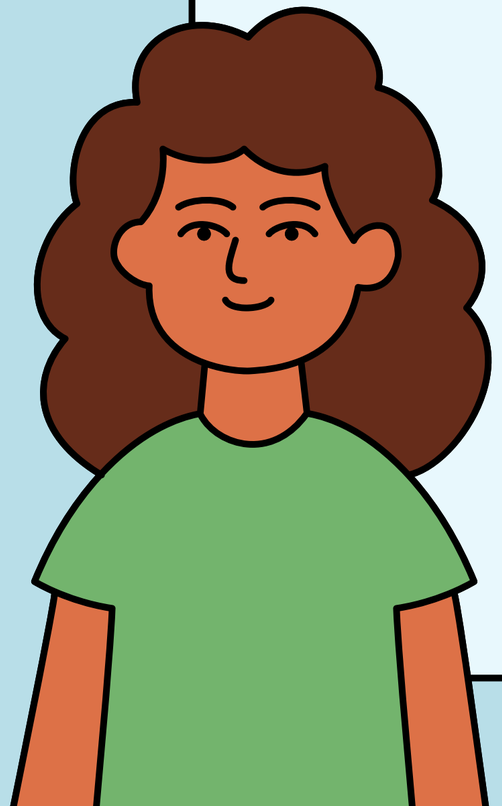

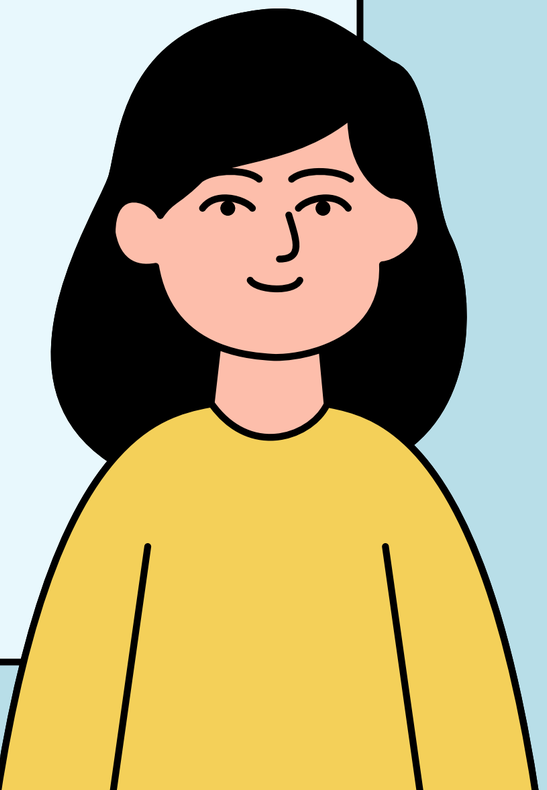

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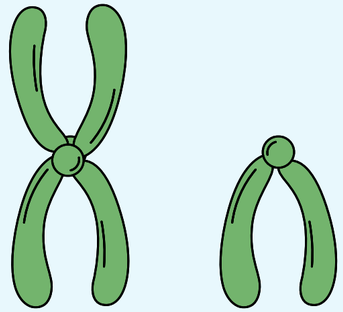

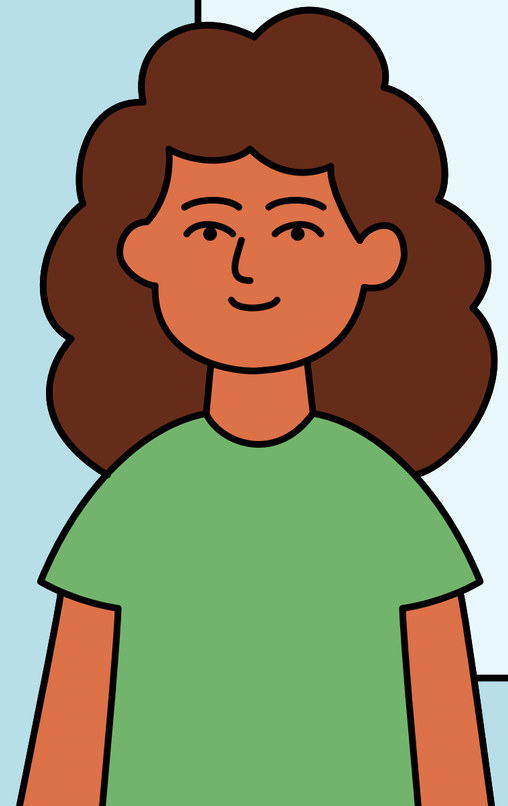

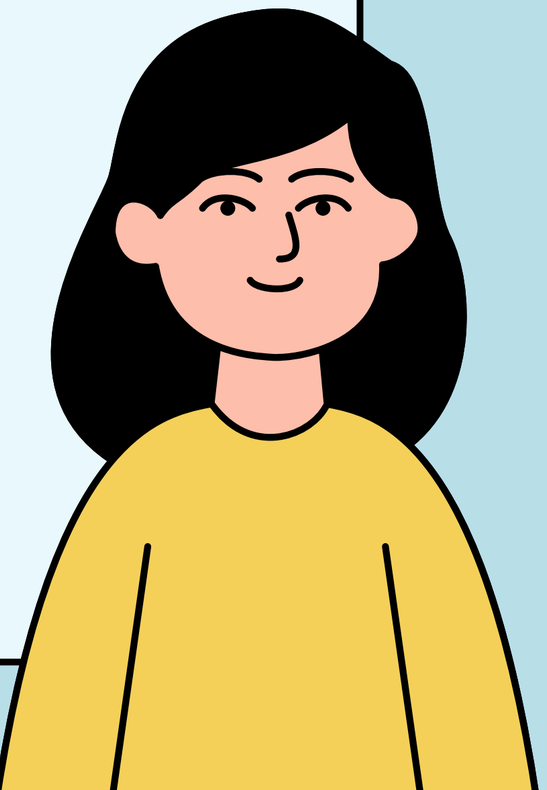

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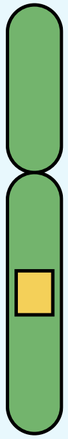
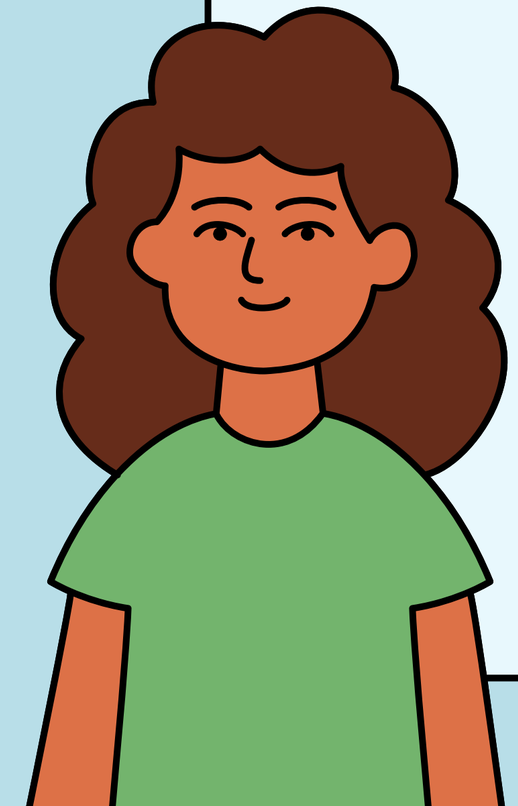
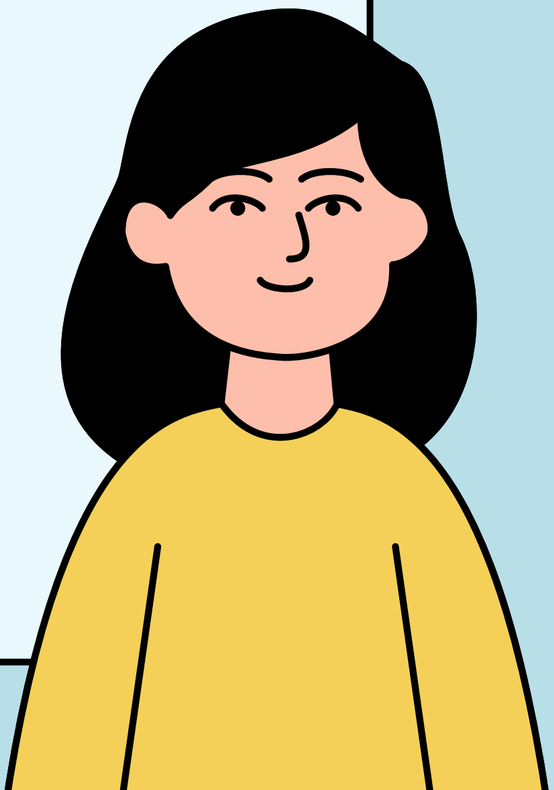
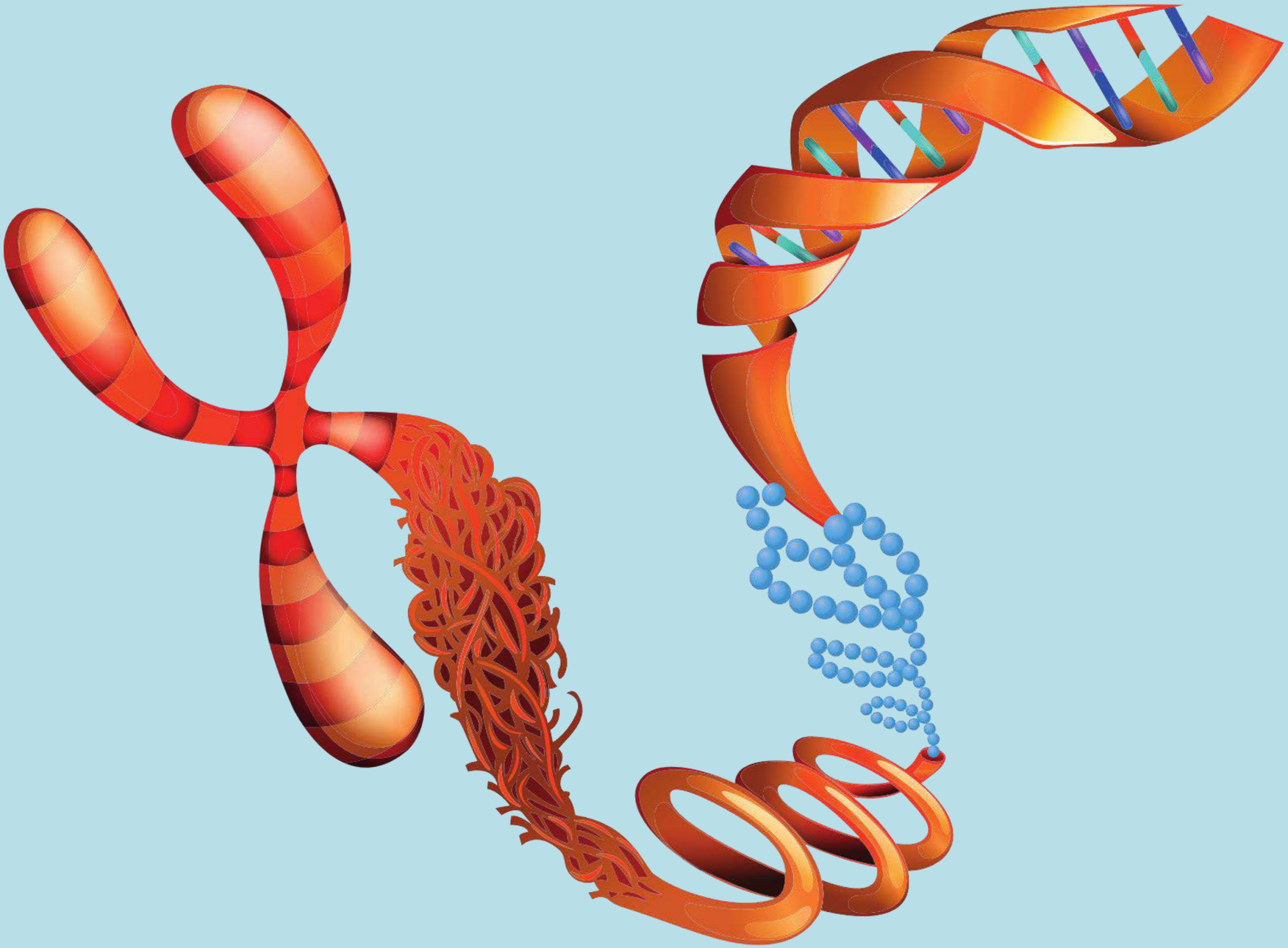


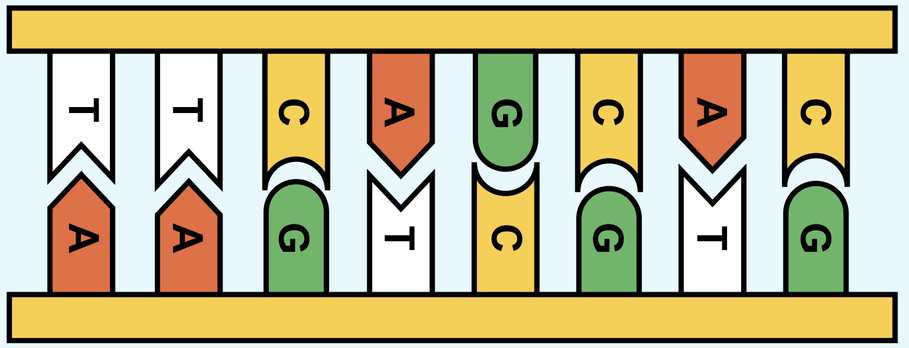






Special investigations

Single gene:
Sequencing change
Base pair deletion or duplication
Triplet repeat
Methylation changes



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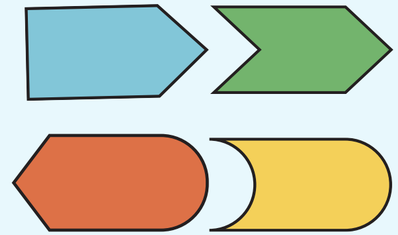

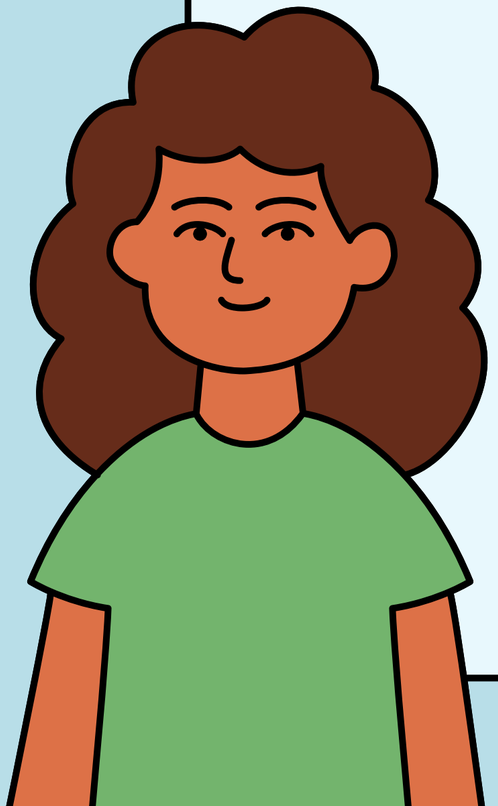

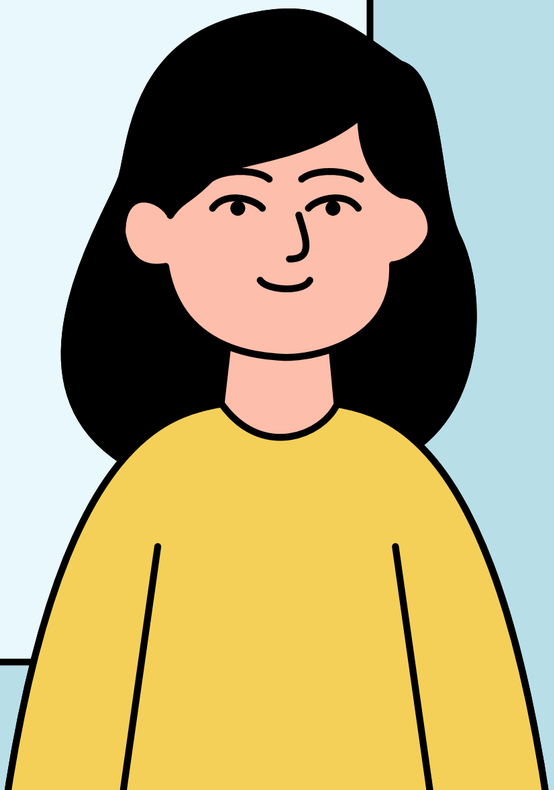

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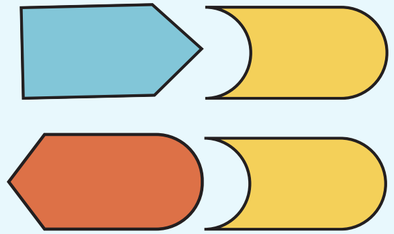

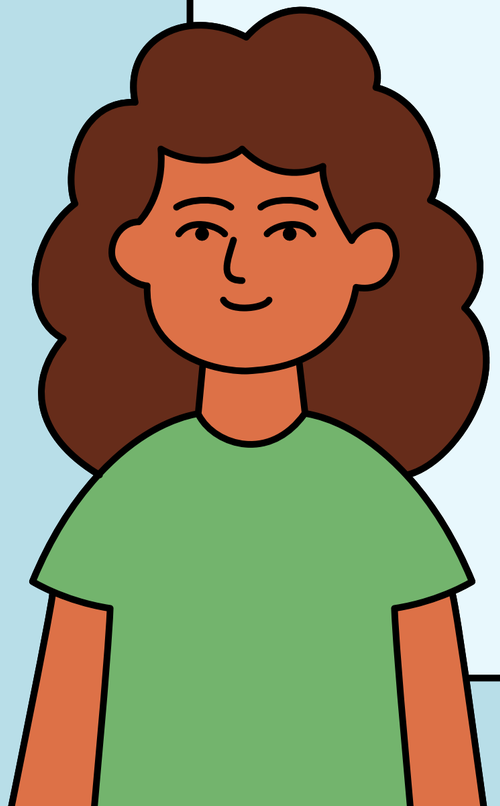

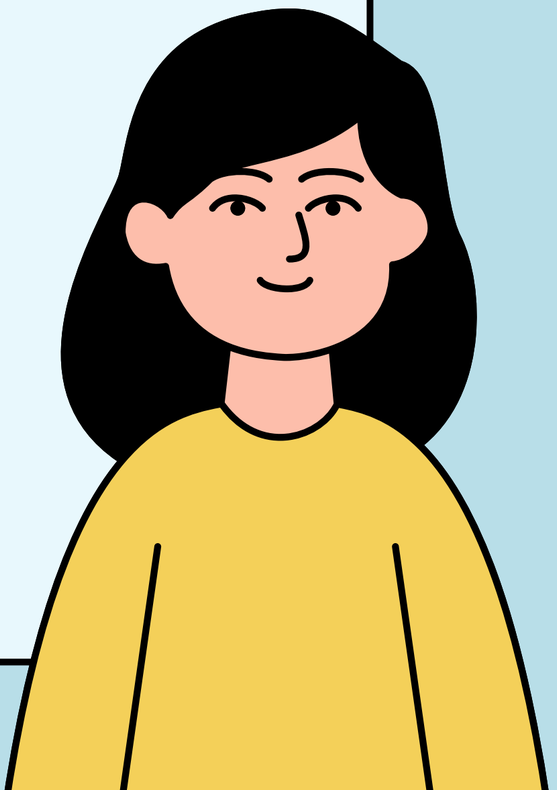

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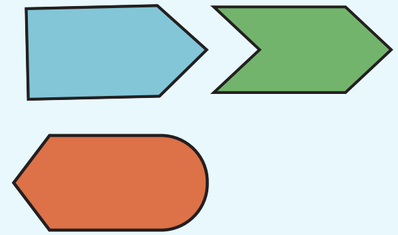

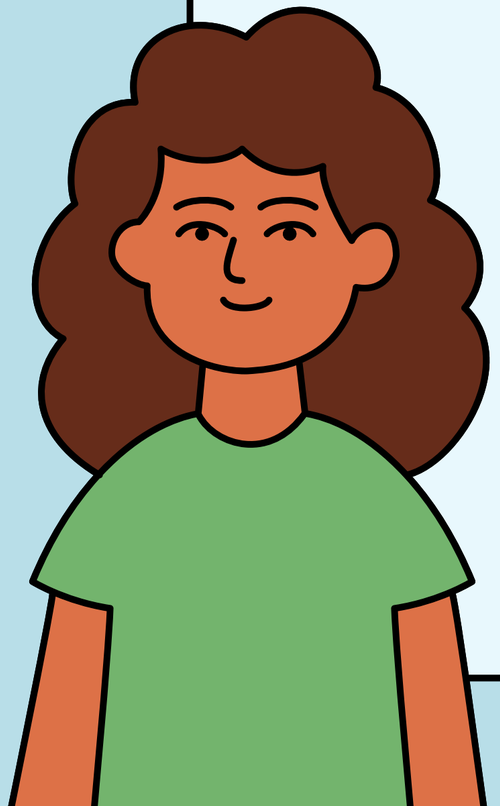

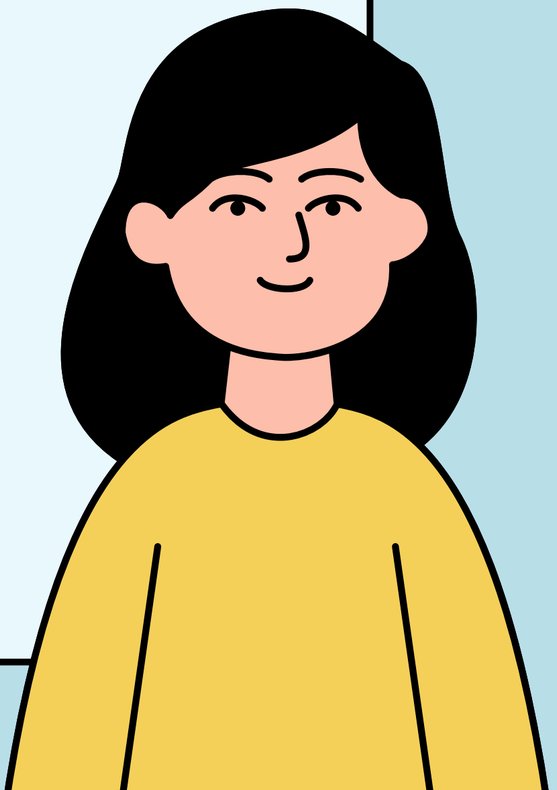

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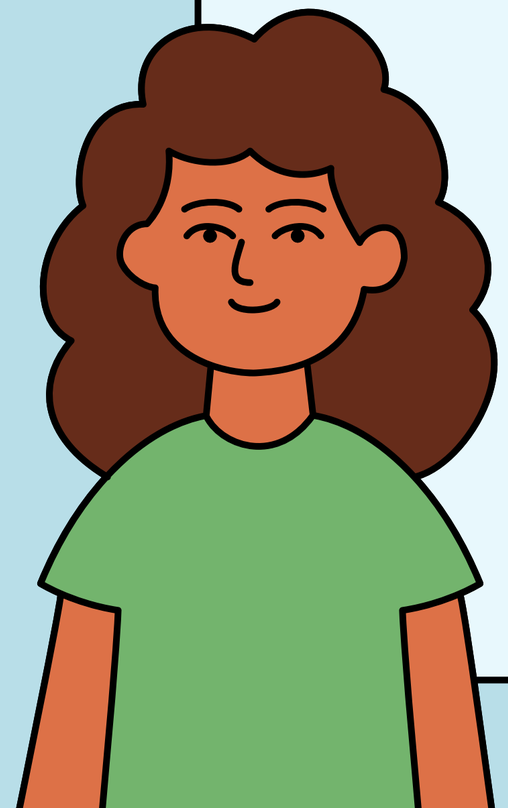

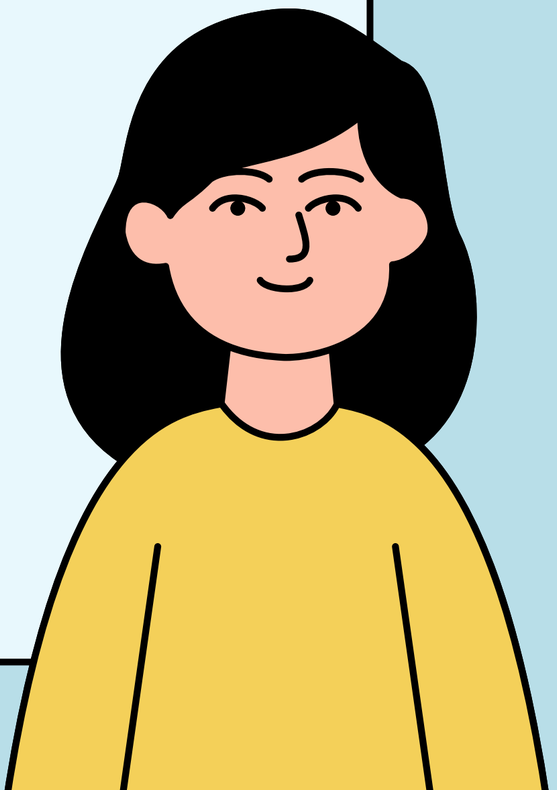

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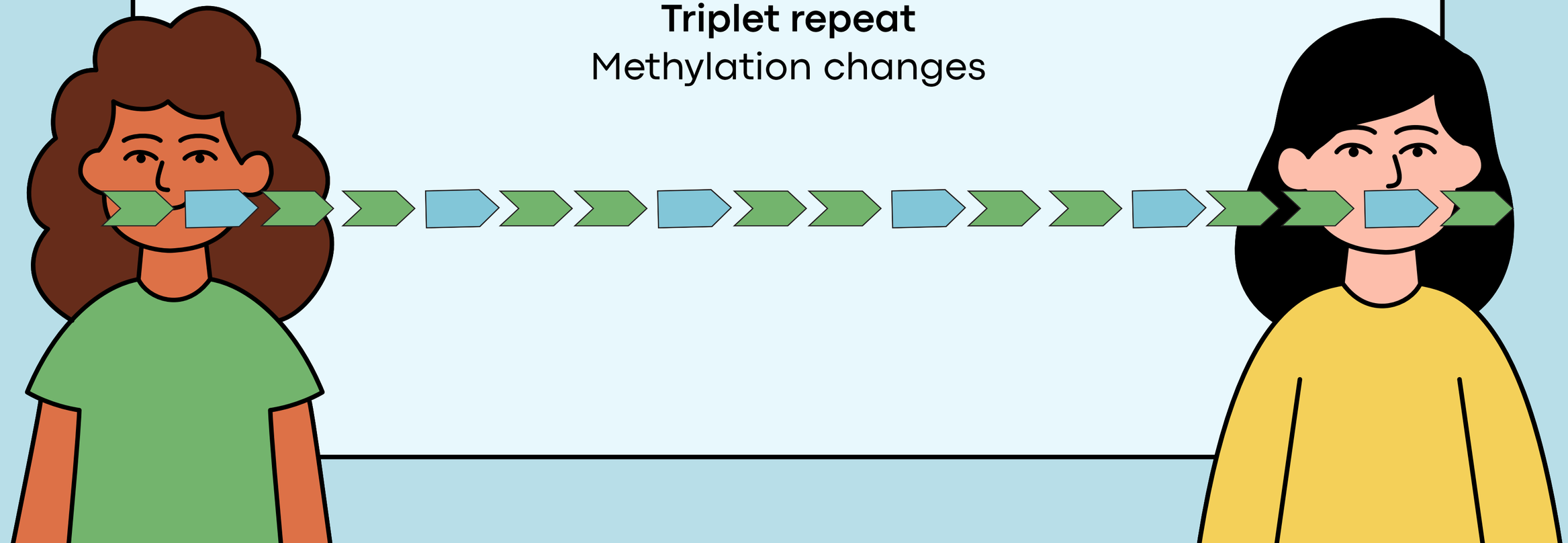

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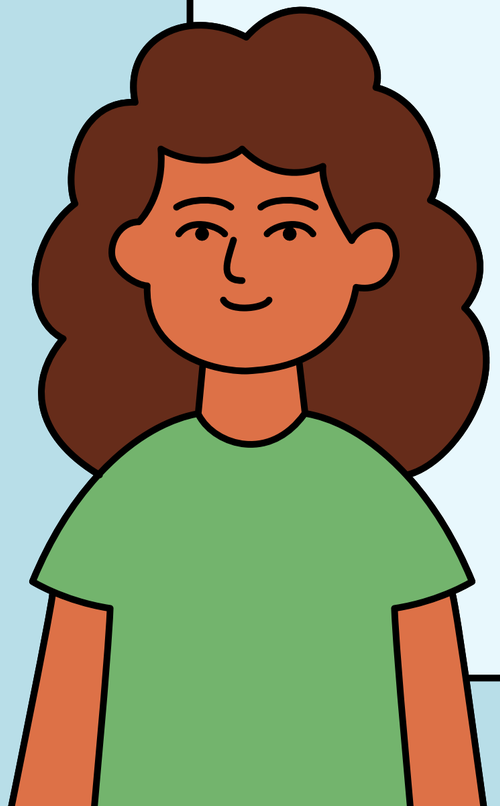
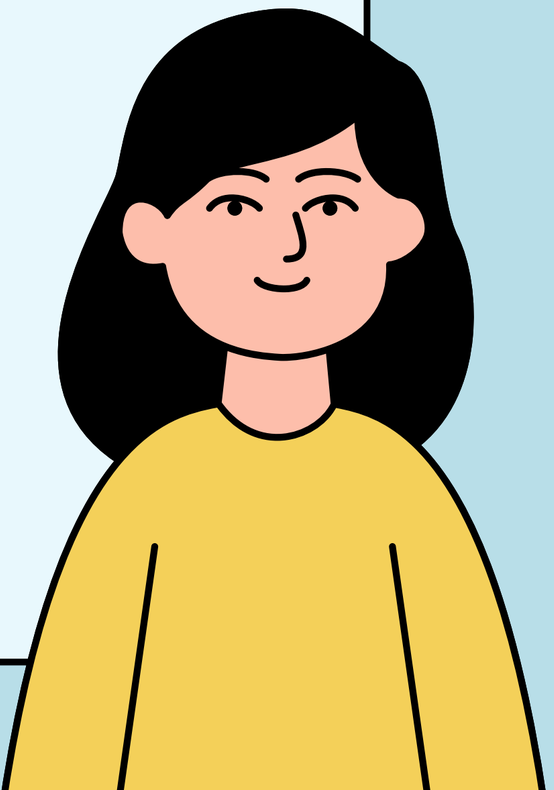


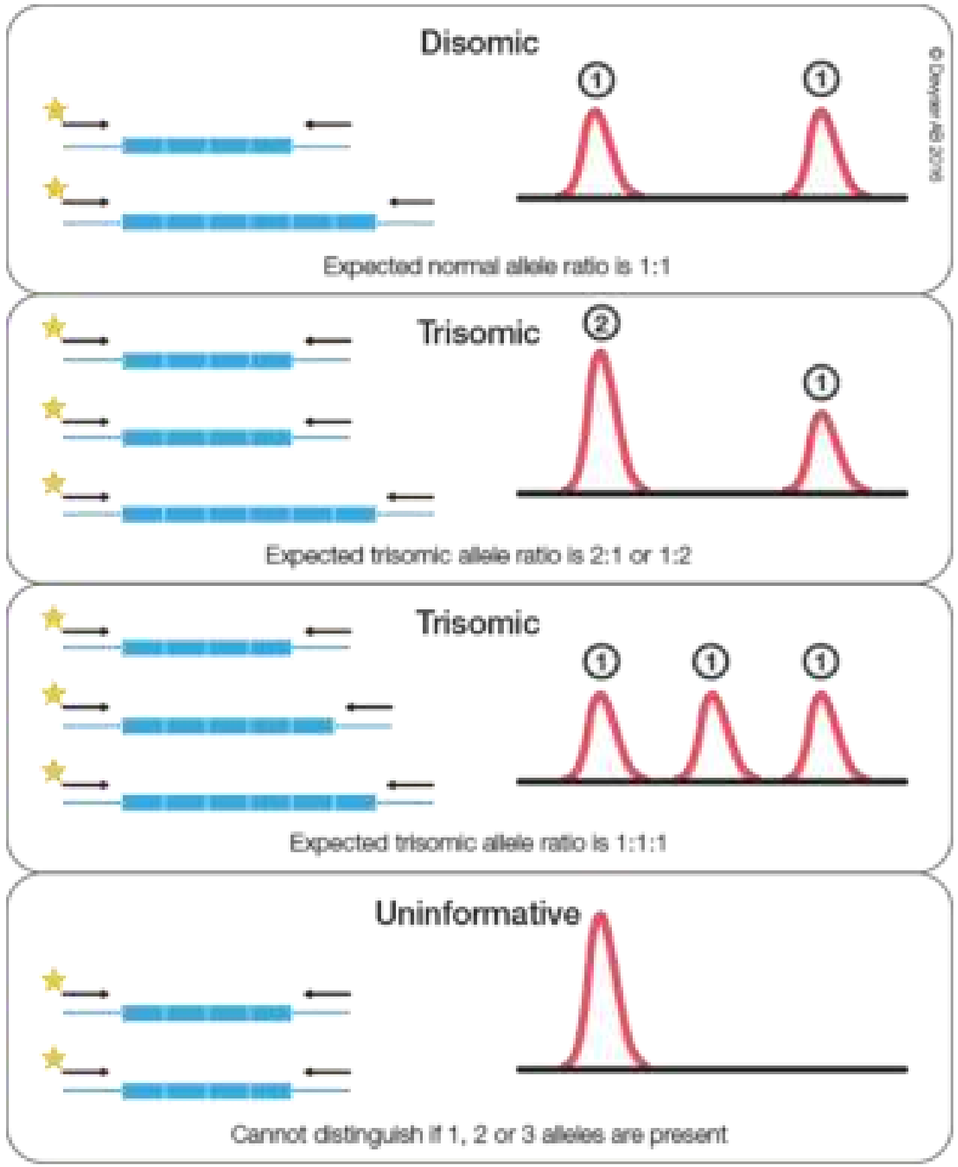


DOSAGE TESTING

QFPCR
Karyotype
Micro-array
MLPA
FISH

Uses amplification, detection and analysis of chromosome-specific DNA sequences known as genetic markers or small tandem repeats (STRs).

Benefits: quick, inexpensive
Limitations; only trisomy 13,18,21 and X, Y. Only dosage



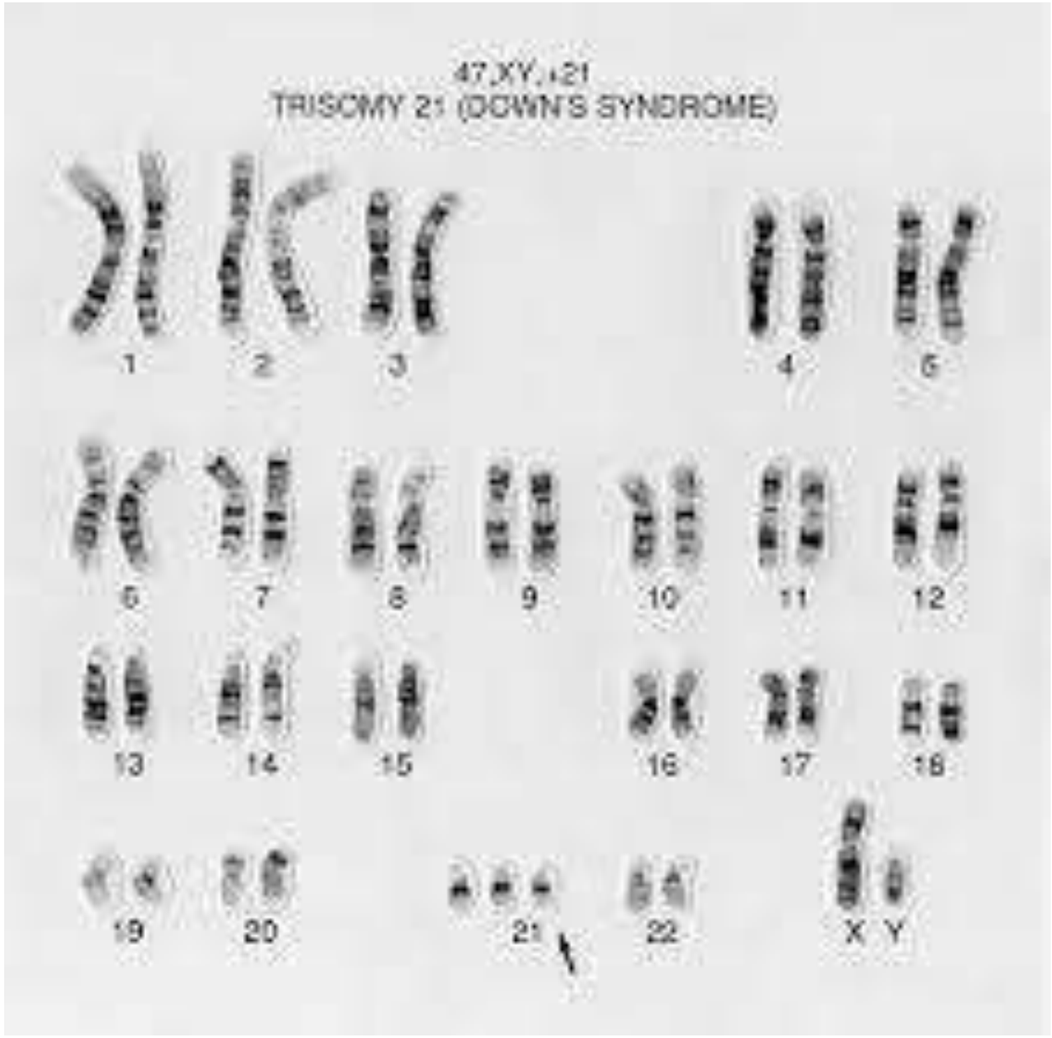
https://devyser.com/blog/principles-of-qf-pcr

DOSAGE TESTING

QFPCR
Karyotype
Micro-array
MLPA
FISH

Analysis of all 46 chromosomes for large structural or numerical abnormalities
Resolution = 8-10Mb

Benefits: all 46 chromosomes, structural and numerical, quicker than array
Limitations: low resolution, no single gene



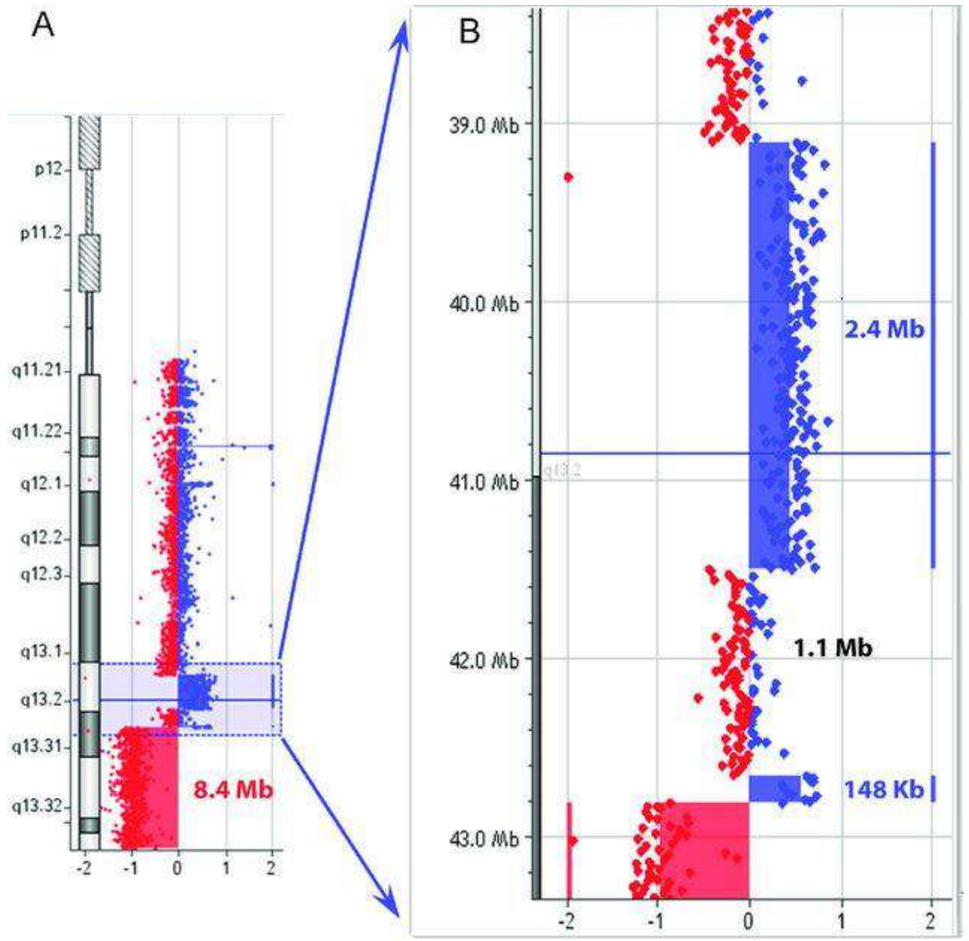
Down syndrome human karyotype 47,XY,+21. Wessex Reg. Genetics Centre. Attribution 4.0 International (CC BY 4.0)

DOSAGE TESTING

QFPCR
Karyotype
Micro-array
MLPA
FISH

SNP and CGH
Dosage abnormalities across all 46 chromosomes
Resolution = 50 - 150kb

Benefits: small deletions and duplications acros all 46 chromosomes
Limitation: only dosage, no structural



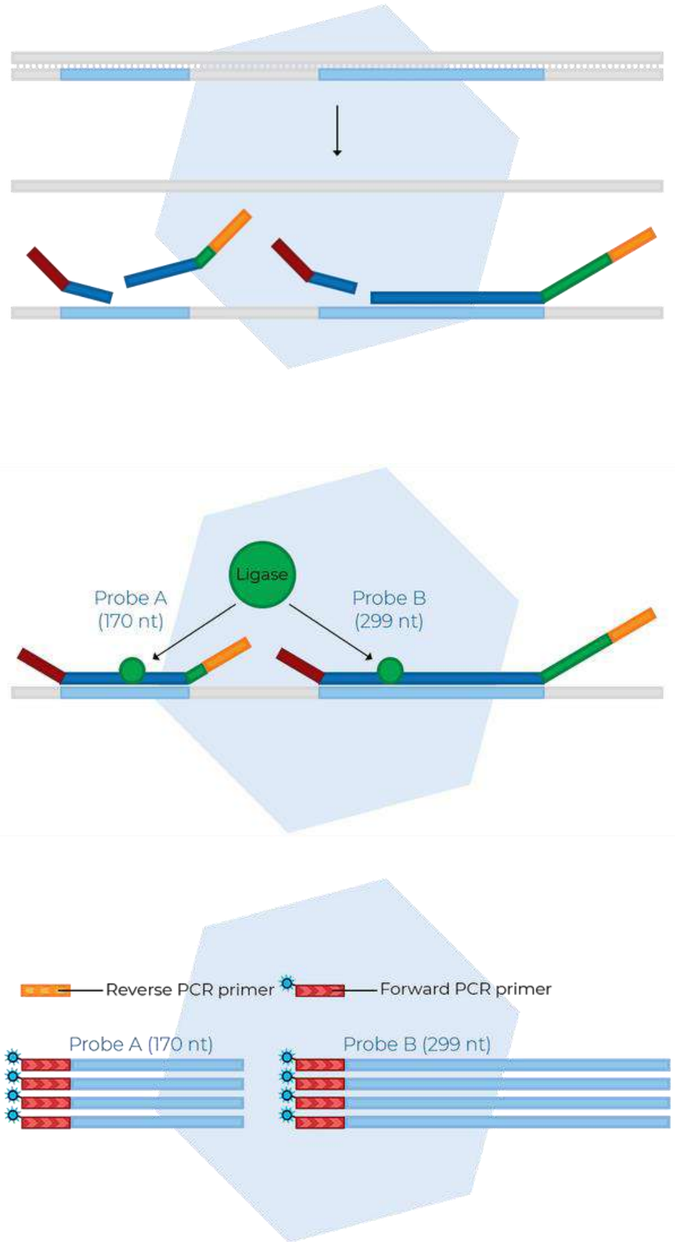
Chromothripsis and ring chromosome 22: a paradigm of genomic complexity in the Phelan-McDermid
syndrome (22q13 deletion syndrome). Kurtas et al. Journal Medical Genetics. 2018

DOSAGE TESTING

QFPCR
Karyotype
Micro-array
MLPA
FISH

Multiplex ligand-dependent probe amplification
Analyses the copy number of up to 60 fragments

Benefits: Broad coverage, small deletions and duplication
Limitations: only tests for what is on the assay

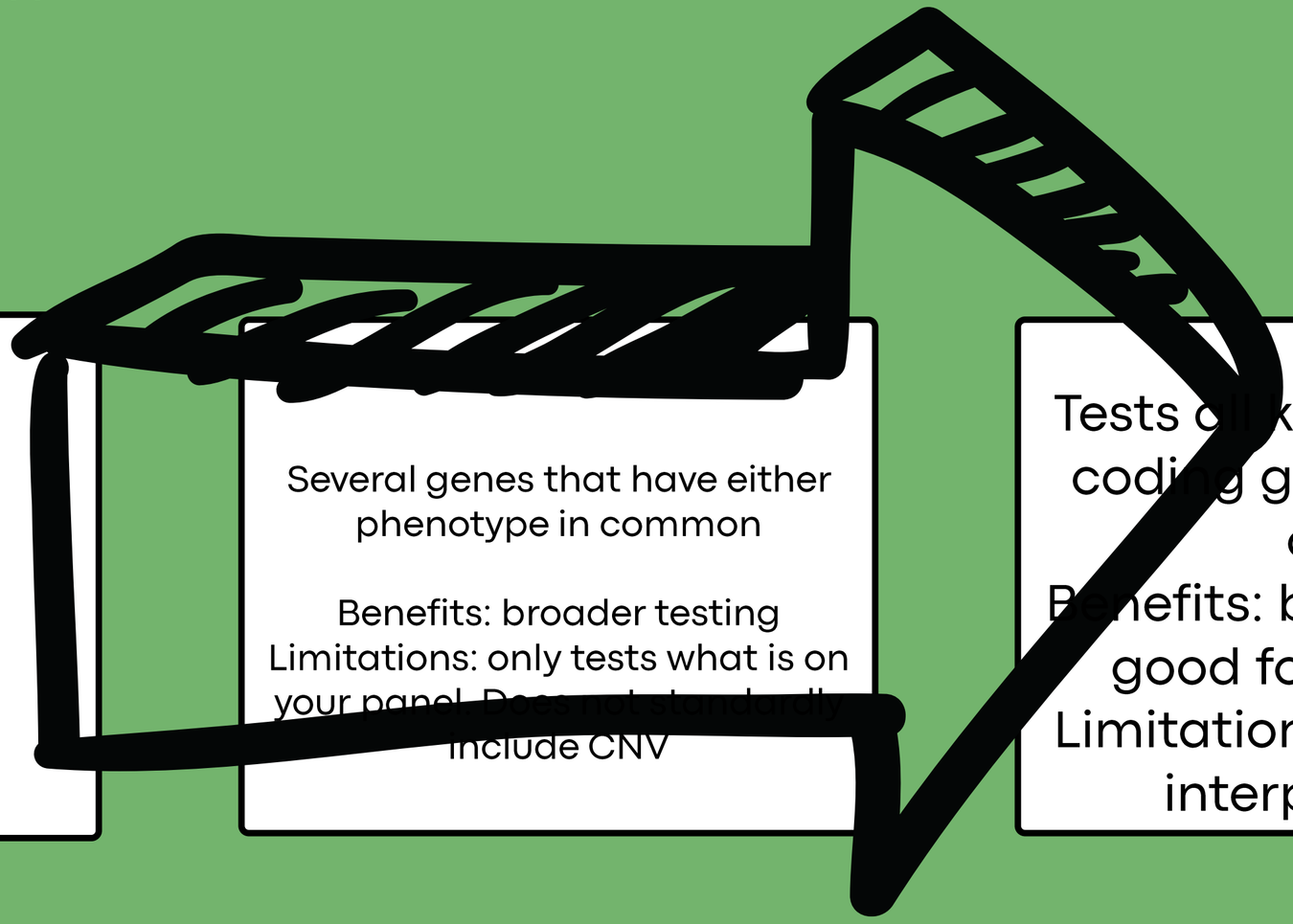


https://www.mrcholland.com/technology/mlpa/technique

SEQUENCING TESTING

Massively parallel sequencing technology that offers ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA

Next generation sequencing



Single gene

Looking at one gene only

Benefits: good coverage
Limitation: only one gene

Several genes that have either phenotype in common

Benefits: broader testing
Limitations: only tests what is on your panel. Does not standardly include CNV

Tests all known protein coding genes - exons only

Benefits: broad testing, good for unknown
Limitations: VUS, data, interpretation

WHAT SHOULD I REQUEST?

- What am I worried about?
- What are the limitations of my test?
- What will it benefit?
- What will the implications of positive, negative and uncertain result be?

SCENARIO 1

History:
Mom's sister had isolated cleft lip
Well grown
No other structural abnormalities
Good suck

SCENARIO 2

History:
42 year old mom
Overlapping fingers
Clubfeet
IUGR
Cardiac murmur
Poor suck
Hypotonia

SCENARIO 3

History:
20 year old well mom
Normal growth parameters
Cardiac murmur
Prominent fingerpads
Facial dysmorphism

SCENARIO 1

Multifactorial
No testing

SCENARIO 2

Trisomy 13

QFPCR
Karyotype
Array

SCENARIO 3

Syndromic

???

SCENARIO 3

Literature search

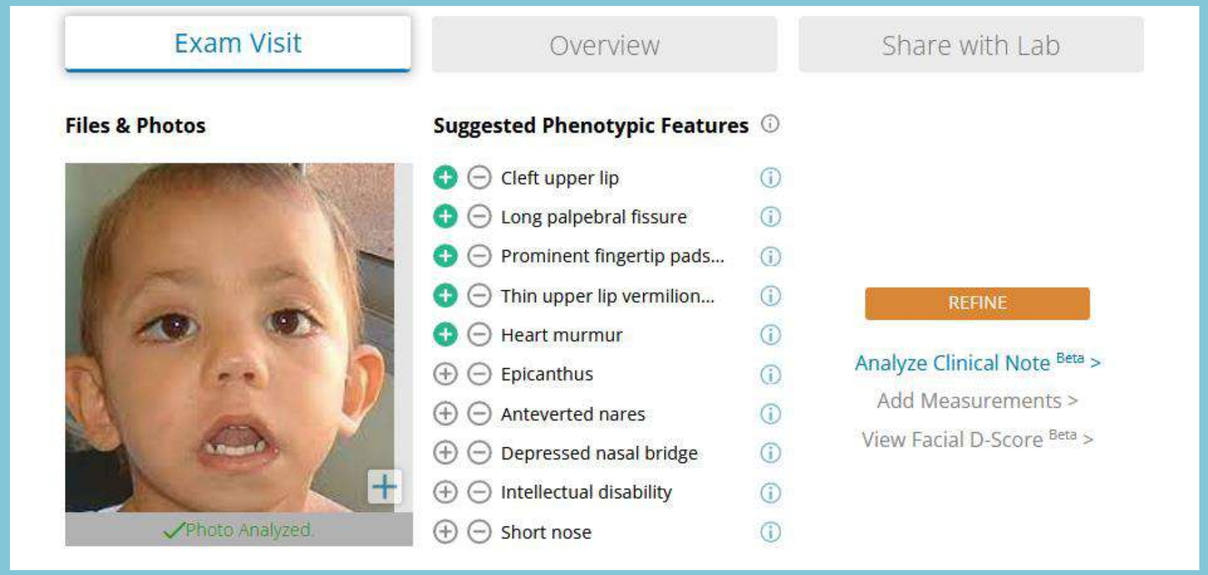
Appropriate investigation

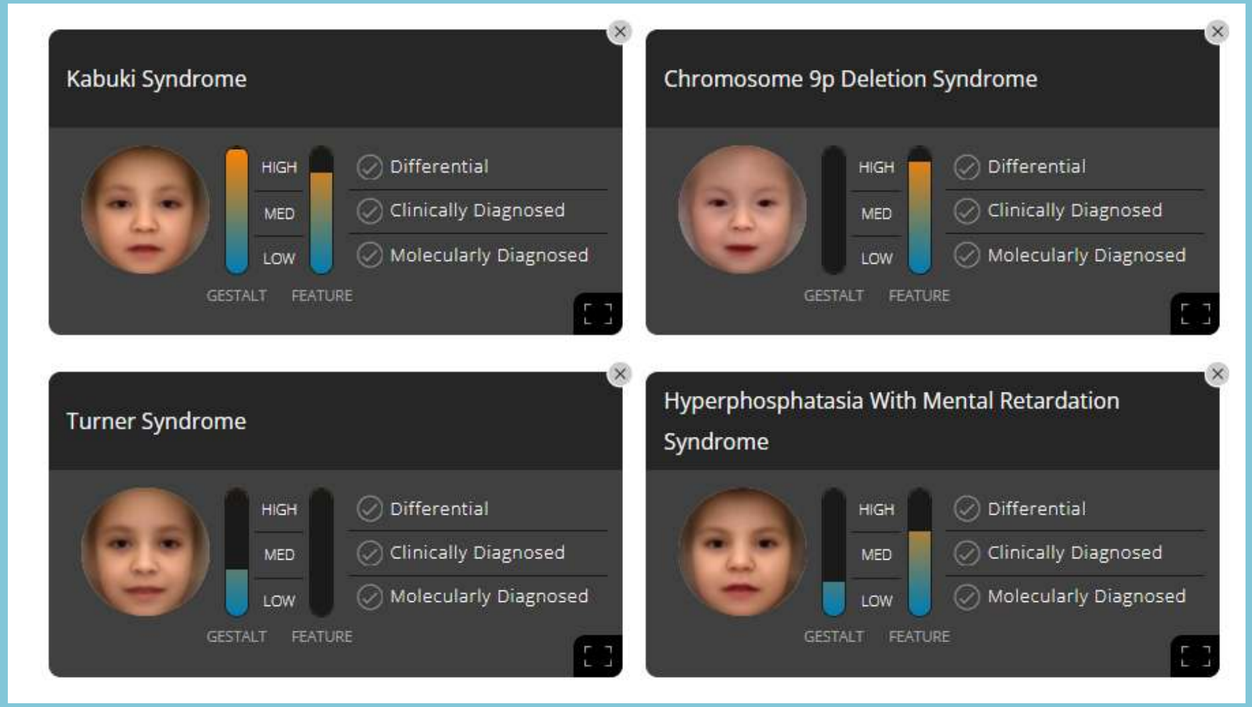
Reading regarding condition

Helpful databases

OMIM	Free online database detailing all know Mendelian conditions. Search functions include: features, genes, conditions
Pubmed	Search group of conditions or individual clinical "hooks" or specific syndrome
Face 2 gene	AI self-learning program that uses facial features to make suggestions WARNING: USE WITH CAUTION
Phone a friend	

https://app.face2gene.com/





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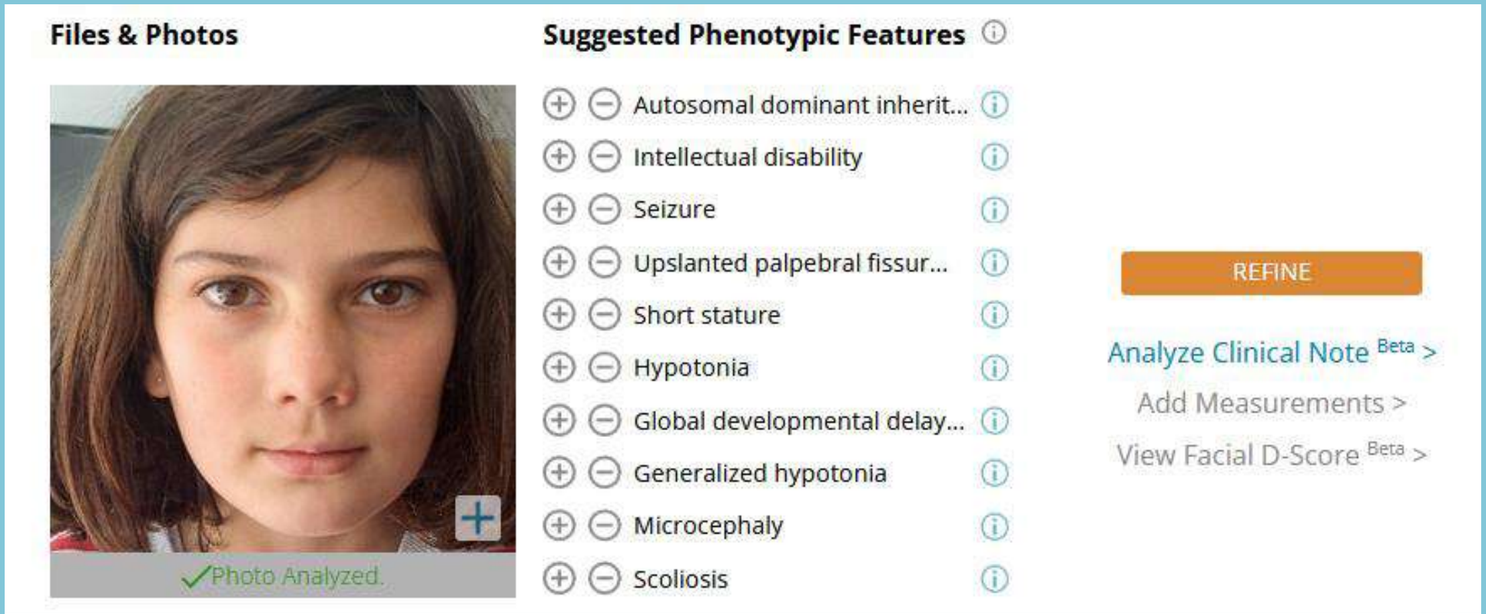
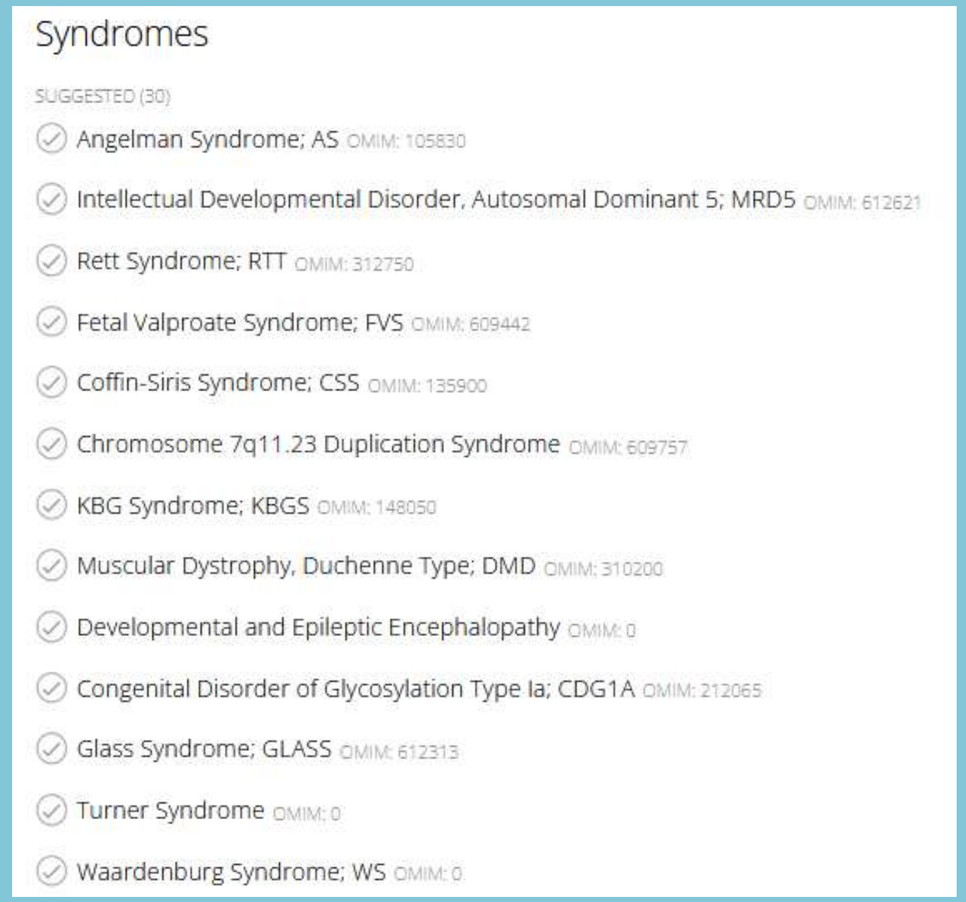
What testing do you do?

ⓘ Start presenting to display the poll results on this slide.

https://app.face2gene.com/





TAKE HOME MESSAGE

- Dysmorphology examination NEEDS a comprehensive approach – history, examination, investigations
- Beware of jumping to conclusions
- Know your normal from your abnormal
- Be meticulous - "clinical excellence"
- Database and literature review
- Know what testing can and can't do

RESOURCES

Dysmorphic neonate: An approach to diagnosis in the current era. Tewari et al. Pediatric dimensions. 2016

Evaluation and diagnosis of the dysmorphic infant. Jones et al. Clinical perinatology. 2015

Genetic counselling approach

Join at

slido.com

#3827 446

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You need to discuss a newborn's dysmorphic features with a new mother. What are your thoughts/feelings going into the interaction?

ⓘ Start presenting to display the poll results on this slide.

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I feel confident talking to parents about dysmorphic features I have noticed in their newborn (rate 1-5).

ⓘ Start presenting to display the poll results on this slide.

Breaking “difficult” news

**“Let not your ears despise my tongue forever,
which shall possess them
with the heaviest sound
that ever yet they heard.”**

Macbeth, Act IV, Sc.3,
Shakespeare

Authors personal account of delivering “bad news” as a resident:

“my mind wandered to what I perceived as an anxiety-producing challenge: I had never been the one to present to a family the information on what I considered to be an overwhelming and serious diagnosis. In fact, I recollect being reasonably distracted during rounds by the upcoming event.”

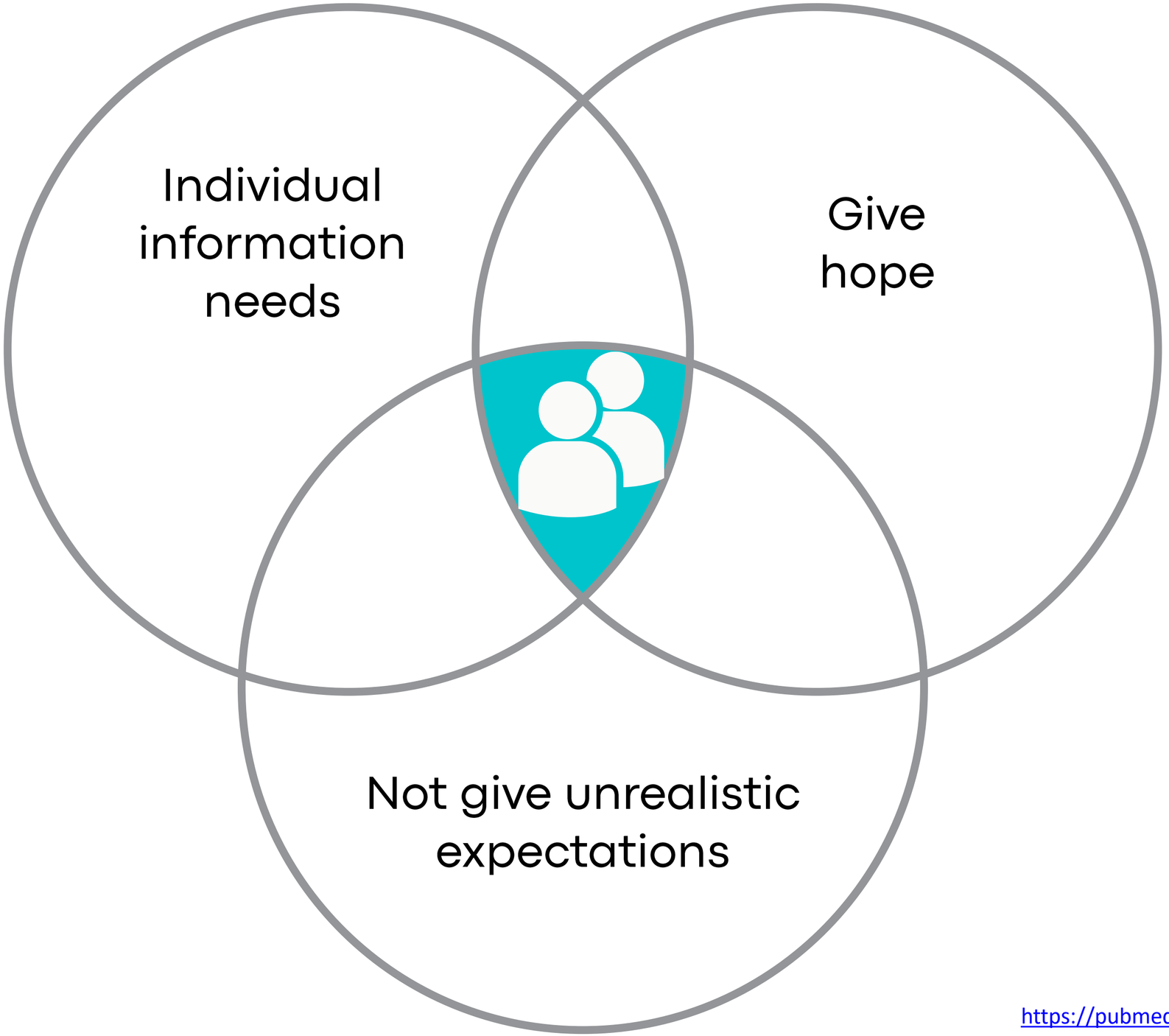
“As I walked from the NICU to the Well Baby side, I had the sense of being unprepared; yes, I was ready to take care of the baby with cyanosis or hyperbilirubinemia, but this was a novel challenge.”

“I have only vague memories of walking in the room and exactly how I introduced myself to the family of this 12-hr-old infant with presumed Down syndrome. My own cursory examination confirmed the clinical suspicion of my colleagues. I recall reporting a few sentences that related our concern of the diagnosis and perceiving a rather rapid change in the affect of both parents. I can still see their faces more than 30 years later.”

“My clinical guess now is that my own nervousness likely conveyed a lack of sensitivity or caring on my part. Whatever the case might have been, my memory of the parents' shock and particularly the anger in the father still stay in my imprint.”

“I do not really know if my own manner and presentation played a minor or significant role in this defining moment for these parents in 1973. What I do know and still am clear about is that as a second-year pediatric resident I had been given no instruction or guidelines as to how to rise to this occasion. The event was defining for me.”

Dent & Carey; (2006) Breaking difficult news in a newborn setting: Down syndrome as a paradigm. AJMG. http://doi.org/10.1002/ajmg.c.30100



https://pubmed.ncbi.nlm.nih.gov/20148936/

Value words – “Bad” news

SPIKES – 6 step-protocol (Baile et al., 2000)

(1) *Setting* up the interview,

(2) assessing the patient’s *Perception*,

(3) obtaining the patient’s *Invitation*,

(4) giving *Knowledge* and information to the patient,

(5) addressing the patient’s *Emotions* with empathic response,

(6) *Strategy* and *Summary*.

Bad news – inherent value in the title!

“any news that drastically and negatively alters the patient's view of his or her future.”
- Buckman 1992

“situations where there is either a feeling of no hope, a threat to a person's mental or physical wellbeing, a risk of upsetting an established lifestyle, or a message that is given which conveys to an individual fewer choices in his or her life.”
- Bor *et al*., 1993

Who determines it is “Bad” news?

“Difficult” news may better describe unexpected or unwelcome info

Table I. Consensus Recommendations for Breaking Bad News

Recommendations
People
Support network: Identify and have present at patient's request
Message
What is said
Preparation: Give a warning shot
Find out what patient already knows
Convey some measure of hope
Acknowledge and explore patient's reaction and allow for emotional expression
Allow for questions
Summarize the discussion: Verbally and/or in written form, audiotape consultation
How it is said
Emotional manner: Warmth, caring, empathy, respect
Language: Simple, careful word choice, direct, no euphemisms or technical diagnostic terminology, avoid medical jargon
Give news at person's pace, allow them to dictate what they are told

Reprinted with permission from Ptacek JT and Eberhardt TL. Breaking Bad News; A review of the literature. 1996. *JAMA* 276:496-502 American Medical Association.

Dent & Carey; (2006) Breaking difficult news in a newborn setting: Down syndrome as a paradigm. AJMG. http://doi.org/10.1002/ajmg.c.30100

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Cardiac murmur
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Hypotonia

SCENARIO 3

History:
20 year old well mom
Normal growth parameters
Cardiac murmur
Prominent finger pads
Facial dysmorphism

Counselling example

- “Good news”
- “Nothing else that I can see that is a concern”
- “She is likely to be just like your sister”

- Patient response – Bursts into tears

- What is happening here?

SCENARIO 1

Perspective

NOT good news

Fears

What will my child go through?

Patient experiences

Remembers what her sister went through
Delayed surgery and difficult repair
Stigma and teasing relating to scar, caused trauma and depression

Don’t know what to expect/uncertainty

Surgery
Feeding/bonding
Future psychological impact

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What could you do differently?

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What to do differently

- Is there someone else you would like with you?
- How are you feeling?
- How was it to see your baby initially post delivery?
- You mentioned your sister had a cleft lip, can you tell me what her experience was like.
  - Acknowledge experiences
  - Correct misconceptions
  - Reassure about care based on story
- We do not see any other concerns for [baby name] – reassure don't expect other challenges - Acknowledge the positive/inherent value of the newborn
- Support group referral

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Counselling Aspects

- Clinical suspicion of a life-limiting illness
- How much do you introduce and when?
- Important diagnosis as it may alter management

- How do you deliver this “difficult news”?

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How would you deliver a strongly suspected diagnosis of Trisomy 13?

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SCENARIO 2

Reaction

Angry and inconsolable

Balancing Act

Realistic but not abandoned

Patient experiences

Feelings of guilt as “her fault” (AMA)
Why was this missed on Ultrasound
Uncertainty of lifespan/ what to expect
Baby “left to die”

Support systems

Family support
Religious or cultural support
Medical staff (nurses or other) – Palliative care

A parent’s story – Marianne

http://www.tellingstories.nhs.uk/index.php/edwards-syndrome/191-mariannes-story

Lesson’s learnt: Mariannes story

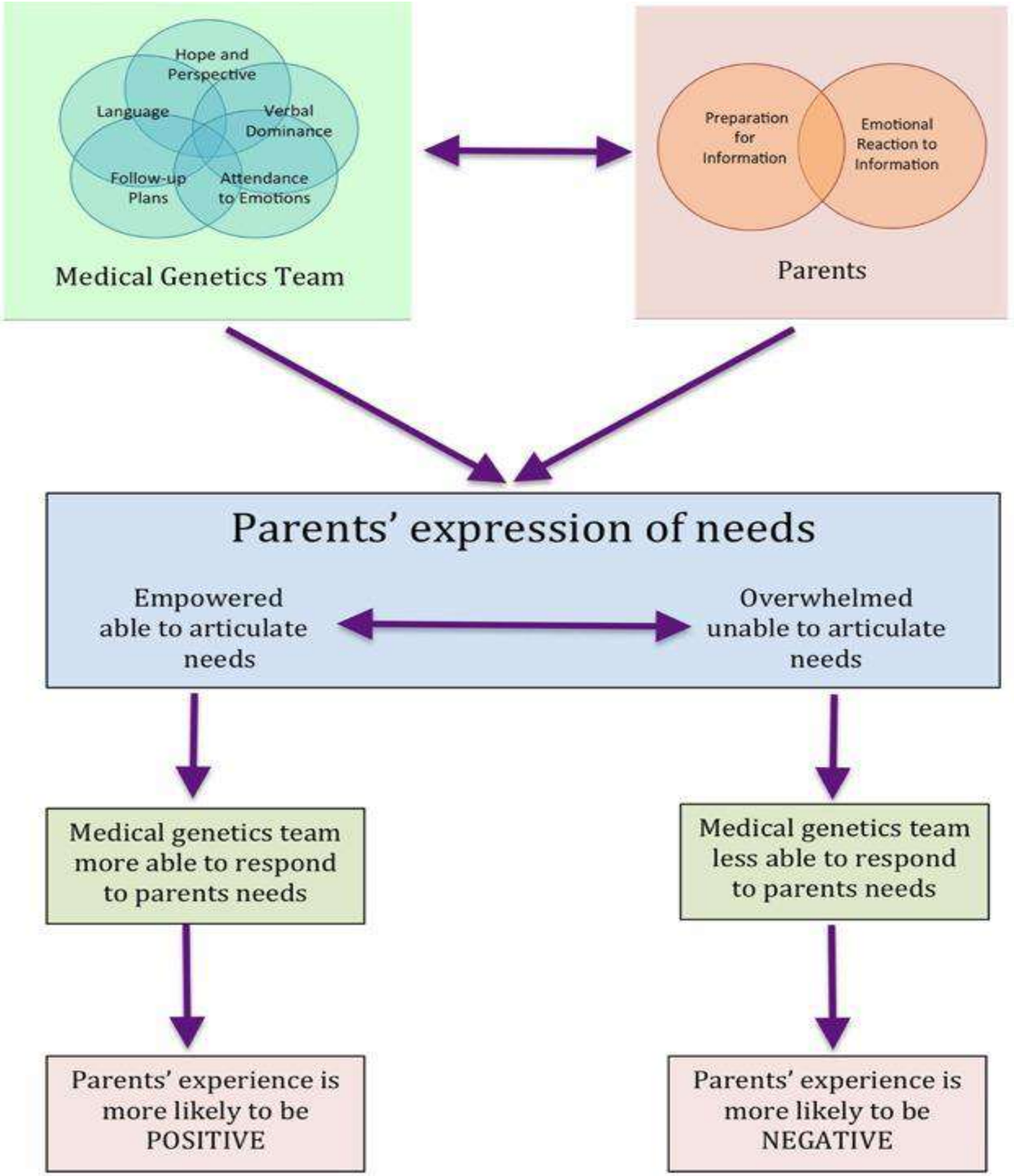
"I was told that they were checking for chromosomal abnormalities and that they were sending off for FISH, which we had no idea what that meant at the time“

"He had Edwards…it was like the seas parting because everybody blanked him, they didn’t want anything to do with him".

"When you hear your child’s going to die, you only need to hear it the once, you don’t need to be told it over and over again, because some people don’t think you’re actually listening to what they’re saying…I think that’s something that really needs to be heeded by the healthcare professionals….be very, very aware because we have to live with this for the rest of our lives and the choices we make to fit with us very comfortably, to make sure that we ’ve done everything possible for our child“

"It’s just….getting over tha being positive, being reali families have hope not just it away from them. People t that with us, you know, ‘he’s g so why are you bothering?’ We’re going to die so why do any of us bothe that’s the case?"

"As humans we have a life span, some shorter than others, but not less important"



Ashtiani et al. (2014). Parents' experiences of receiving their child's genetic diagnosis: A qualitative study to inform clinical genetics practice. AJMG*164*(6): 1496-1502. Doi: 10.1002/ajmg.a.36525

Parents Experiences

- A Need for Hope

"I was just listening to [the geneticist] in shock but you know, when [s/he] said that [child] can go to school, just like normal, like you know, I felt like that's not so bad. You know, I was just like, not as broken-hearted."

"They could have said… well, just love her, try to teach her. She'll learn something right? Would have been different hearing that… But what we kind of heard was like, she's not going to learn nothing or do nothing. Kind of give up hope on her kind of thing…"

- A Need for a Broader Perspective

"I came out of that feeling like," so what does this mean? "Now what do we do? What is the implication not, dealing with not just, [child's] own physical health but what does it mean for us…"

"in lots of ways, ya, we're reminded about the preciousness of life and how, you know, how value can't be measured in terms of IQ, or, and [our daughter] is very unconventionally smart […] She understands lots of things, surprises us… I guess what I am saying is that it's good to be cautious about the language of this being a big tragedy. Because, there is a whole person there and uh, many good things can come of living with such an unusual person."

Ashtiani et al. (2014). Parents' experiences of receiving their child's genetic diagnosis: A qualitative study to inform clinical genetics practice. AJMG*164*(6): 1496-1502. Doi: 10.1002/ajmg.a.36525

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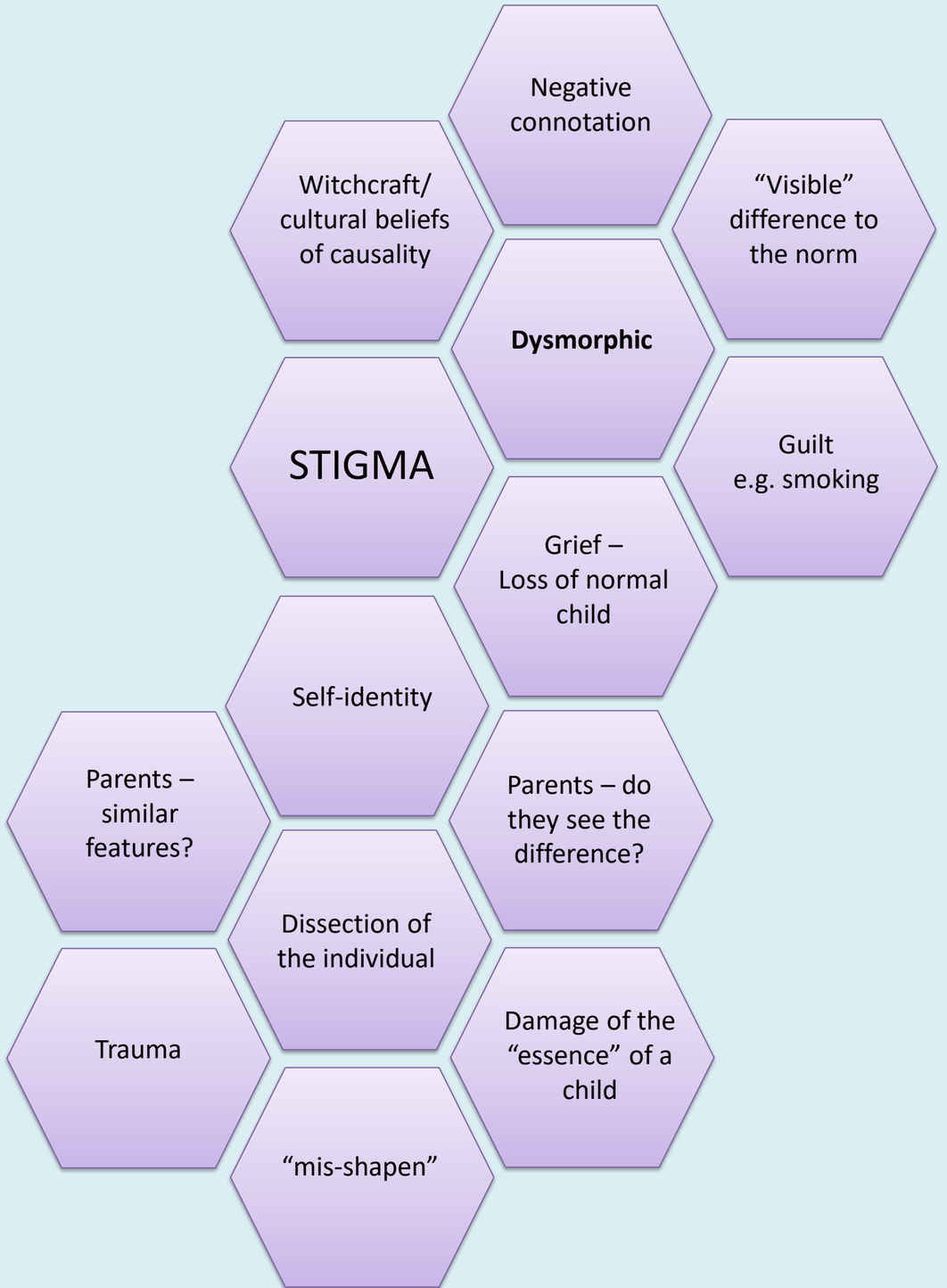
Prominent finger pads
Facial dysmorphism

Too little

Too much

Just right

Value words – Dysmorphic/ dysmorphism



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What feeling/meaning does the word "dysmorphic" bring to mind?

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Drawing attention to difference: Dilemmas in discussing dysmorphism with parents

Susan M White, Jan Hodgson

First published: 06 October 2010 | https://doi.org/10.1111/j.1440-1754.2010.01876.x | Citations: 1

Practical Ideas

1 Start from where the parents are at. It is helpful to establish the parents' perspective on their child's appearance to determine if they have observed the facial differences or if the child resembles members of the extended family. Non-judgemental questions such as 'who do you think your child resembles?' can achieve this.

2 Explain your observations in neutral terms. Use non-medical language and avoid 'jargon' or value-laden terms. Descriptors such as 'distinctive features' rather than 'dysmorphisms' are preferred. One answer to Olivia's mother's question might be, 'I have noticed that Olivia's ears sit quite low on her head, so I was just giving her a general check-over. Do other family members have similar ears?'

3 Explain why diagnoses are important, and the process of syndrome diagnosis, so that parents understand the need for careful observation of physical difference: analogies such as 'looking for clues' or putting together a jigsaw may help. Referring to the example of Olivia, the conversation may proceed as follows: 'Olivia has a few features that are different to both of you (her parents). These will never cause her any health problems themselves, but they can sometimes be part of a genetic condition and associated with other issues, such as being short for her age or sometimes, heart problems. So we try to piece together if there is an underlying condition so that we keep Olivia well and know as much about her health issues as possible.'

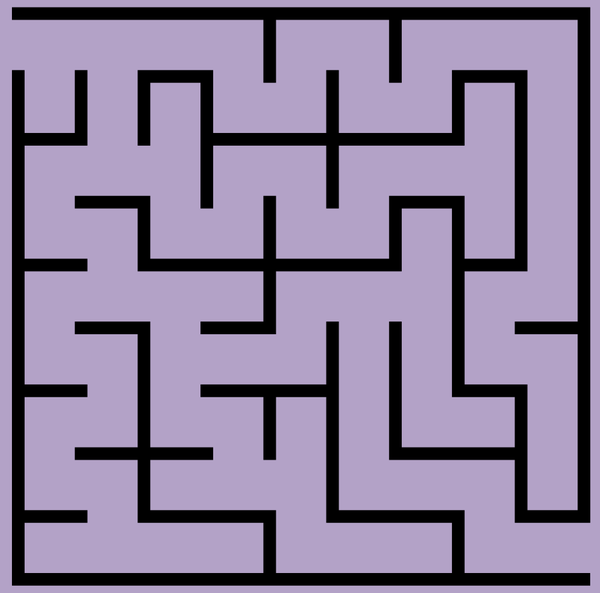
4 Remember the child in the room and where possible, include them in the discussion. Some practitioners would avoid discussing dysmorphism in front of the child, but it is important to be aware of the child's ability to sense the emotional reaction of you and their parents so that removing the child from the room may raise unfounded fears in the child. Other options include sensitive, age-appropriate discussion of features in the child. Where possible, focus on the issues that are identified as problems by the family, such as short stature or learning difficulties, rather than dysmorphism.

5 Watch for parental reactions, knowing that the process of syndrome diagnosis evokes strong reactions in some parents. Explore how parents feel about your observations and be aware of possible harm caused by medicalisation of something that is seen as part of the family. Gently correct any false beliefs.

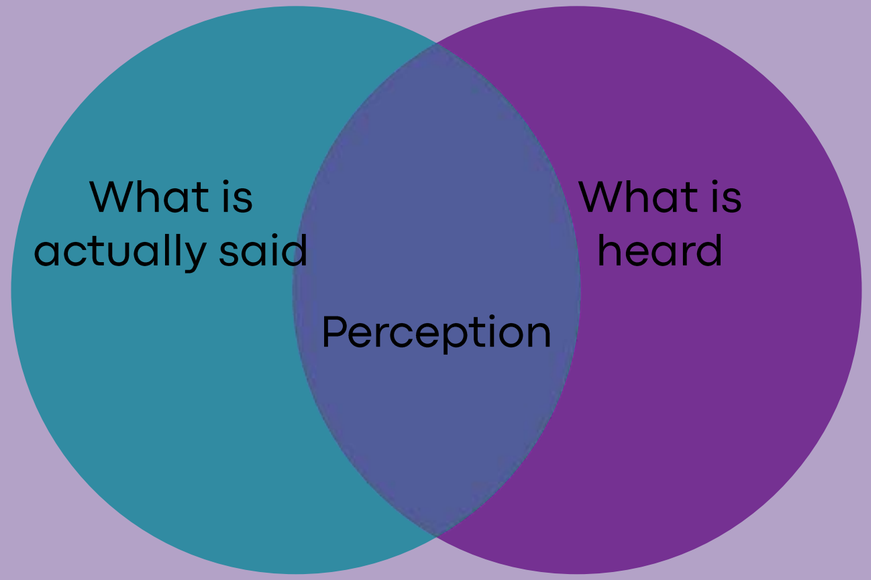
6 Be aware of your own professional curiosity and desire to make a diagnosis and that this may cloud your judgement. While you may wish to be the one to make a prompt and accurate diagnosis, just informing parents of dysmorphism can be devastating for parents and is often unwanted or unexpected news. It is often better to refrain from giving uncertain diagnoses.

7 As paediatricians, we have an opportunity to contribute to greater acceptance of difference in society. One important way to achieve this is by ensuring language use is not stigmatising, is 'person first' and is respectful.

8 Health professionals hone their craft by reflection. Be aware of your own reactions, think about the interaction and discuss with colleagues.



Navigating the space



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What one thing have you taken from today's talk?

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GENETIC COUNSELLORS SOUTH AFRICA

What is GCSA

Professional Focus group as part of the SA Society for Human Genetics

Currently 31 practicing GC's in SA – many do also offer electronic/tele-counselling

Directory of service providers available!

https://sashg.org/genetic_services/

SASHG

Southern African Society for Human Genetics