STUDENT CASE FILE | DEVELOPMENTAL DOMAIN | LESSONS 1 TO 20

The Baby Mateo Case

One observed structural difference. Twenty evidence updates. One bounded clinical synthesis.

Composite patient snapshot

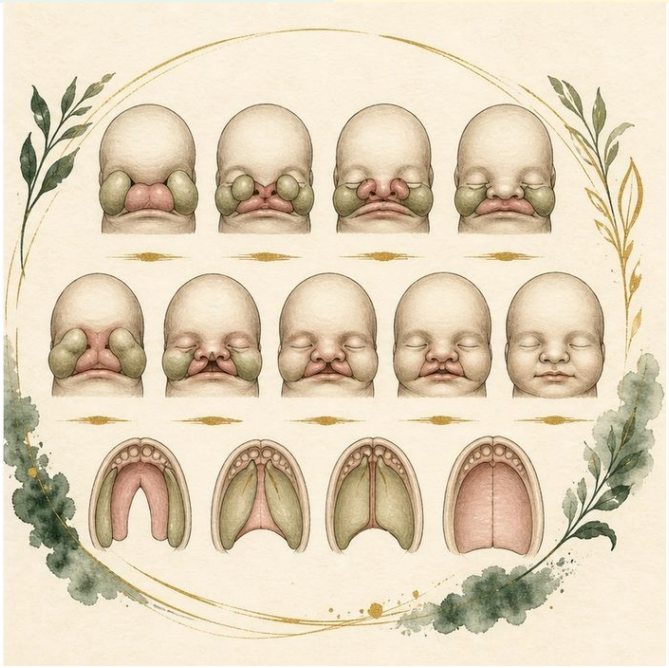
Patient	Mateo, a composite teaching case. No real patient data.
Birth	Term newborn. Breathing and tone are stable.
Observed structure	Complete unilateral left cleft lip and palate.
Initial whole-body exam	No additional congenital anomalies identified on the first structured examination.
Inquiry target	Is the cleft isolated or part of a syndrome? What evidence supports the cause model and care plan?
Evidence rule	Use only the labeled findings supplied in the lesson. Do not invent history, tests, symptoms, or family details.

EVIDENCE SUPPLIED

Every required finding has a stable ID.

EVIDENCE NOT SUPPLIED

Do not invent missing symptoms, tests, exposures, or family history.



Illustration, not a clinical photograph. Composite craniofacial teaching model.

EVIDENCE UPDATE 1 OF 20 | EMBRYOLOGIST

When Could Mateo's Cleft Have Happened?

The lip and palate form in short, ordered windows, so timing narrows where a developmental change began.

Biomedical teaching illustration: Place lip and palate formation on the human timeline

ID	Finding supplied in the case	Why it matters
DEV01-E1	The upper lip normally joins during approximately weeks 4 to 7.	Mateo's cleft lip began during an early facial fusion window.
DEV01-E2	Secondary palate development starts near week 6 and fusion is normally complete by about week 12.	Mateo's cleft palate began during a later, overlapping window.
DEV01-E3	A newborn cleft is the visible result of an earlier developmental event.	The delivery-room appearance does not give the exact day or cause.

Decision in this update: Choose the timeline statement and cite the two evidence cards that set its limits.

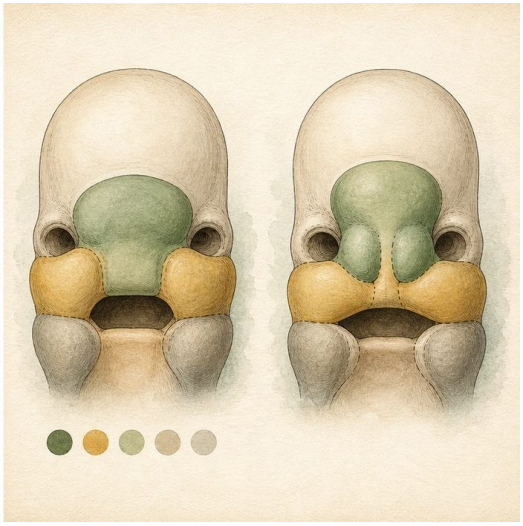
Claim ceiling: You may identify developmental windows. You may not identify an exact day or cause from the cleft pattern alone.

Handoff to the next update: We answered today's question: Mateo's cleft started in a window between about week 4 and week 12. But if a cleft is a fusion that did not happen, then which exact building blocks of the face were supposed to grow toward each other and fuse? We chase that next time.

EVIDENCE UPDATE 2 OF 20 | EMBRYOLOGIST

Which Building Blocks Must Fuse to Make a Lip and Palate?

The face forms when named tissue prominences grow into position and join specific neighbors.



Biomedical teaching illustration: Map the five prominences to the upper lip

ID	Finding supplied in the case	Why it matters
DEV02-E1	One frontonasal, two maxillary, and two mandibular prominences surround the early mouth.	The five prominences are the starting blocks of the face.
DEV02-E2	The maxillary prominence must meet the medial nasal region to build the upper lip.	A failed meeting at this boundary can produce cleft lip.
DEV02-E3	The mandibular prominences mainly form lower-face structures.	They are not the direct lip-fusion boundary in Mateo's cleft.

Decision in this update: Choose the useful label set and defend it with two evidence cards.

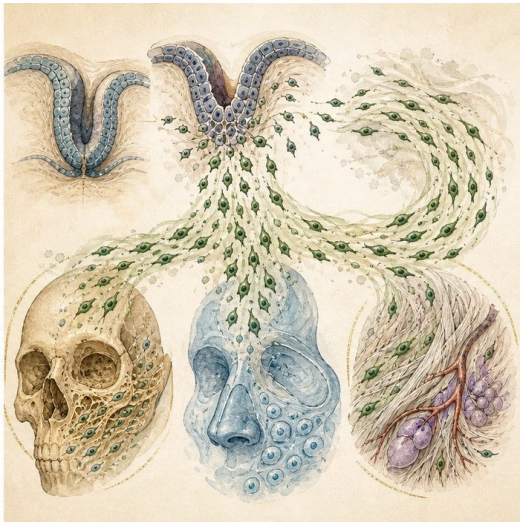
Claim ceiling: You may name the tissue boundary involved in lip formation. You may not name the molecular cause yet.

Handoff to the next update: We named the blocks that must fuse. But each prominence is packed with cells that grow and migrate, and we have not asked where those cells come from. So the next question is: where do the cells that build these facial blocks actually originate? We chase that next time.

EVIDENCE UPDATE 3 OF 20 | NEURAL CREST CELL BIOLOGIST

Where Do the Cells That Build the Face Come From?

Cranial neural crest cells leave the neural folds as flexible builders that can become several craniofacial tissues.



Biomedical teaching illustration: Follow cranial neural crest cells from neural fold to facial mesenchyme

ID	Finding supplied in the case	Why it matters
DEV03-E1	Cranial neural crest cells arise near the closing neural folds.	They share an early origin before entering the face.
DEV03-E2	They undergo EMT and delamination before migration.	They must loosen epithelial attachments and become mobile.
DEV03-E3	Their descendants form much craniofacial bone, cartilage, and connective tissue.	Their early state supports several later fates.

Decision in this update: Choose the correction and cite evidence for both mobility and later specialization.

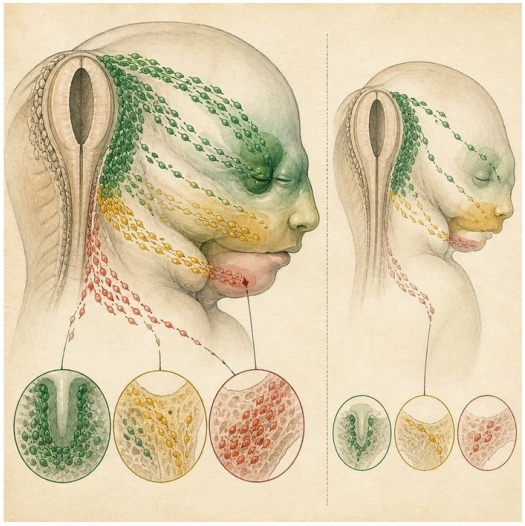
Claim ceiling: You may describe lineage potential. You may not claim that every craniofacial tissue comes only from neural crest.

Handoff to the next update: The face-building cells are born at the top of the embryo, near the brain, and break free by delamination. But the prominences they need to fill sit far away around the mouth and jaw. So the next question is: how do these cells travel from the neural folds to the right facial blocks? We chase that next time.

EVIDENCE UPDATE 4 OF 20 | NEURAL CREST CELL BIOLOGIST

How Do the Face-Building Cells Get to the Right Place?

Face-building cells must travel in organized streams to the right destination before they can build the right structure.



Biomedical teaching illustration: Trace neural crest streams into facial regions

ID	Finding supplied in the case	Why it matters
DEV04-E1	Cranial neural crest cells migrate in reproducible streams.	Their movement has spatial organization.
DEV04-E2	Different streams enter the frontonasal region and pharyngeal arches.	Route and destination are linked.
DEV04-E3	Reduced neural crest survival or migration can cause facial hypoplasia.	Cell number at the destination affects growth.

Decision in this update: Choose the defensible prediction and cite the route and cell-number evidence.

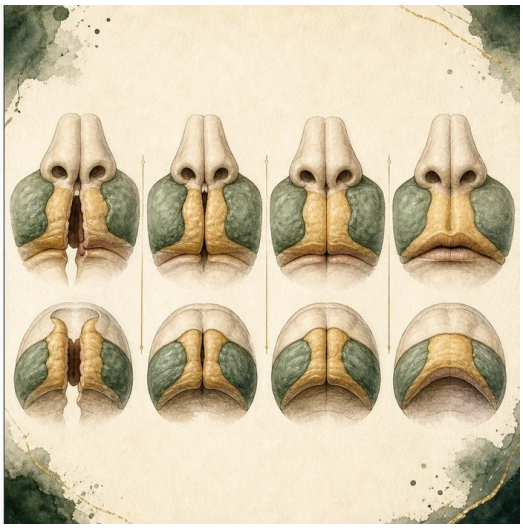
Claim ceiling: You may predict a developmental consequence in the model. You may not diagnose Mateo from one animal image.

Handoff to the next update: The face-building cells ride organized streams into the frontonasal process and the first arch, filling the prominences. But the lip is still open: the blocks have arrived and grown, yet they sit next to one another as separate pieces. So the next question is: how and when do those separate blocks actually close to make a lip? We chase that next time.

EVIDENCE UPDATE 5 OF 20 | EMBRYOLOGIST

How and When Does the Upper Lip Close?

Upper-lip closure requires growth, contact, and stable fusion at the maxillary-medial nasal boundary.



Biomedical teaching illustration: Name the three steps in upper-lip closure

ID	Finding supplied in the case	Why it matters
DEV05-E1	Upper-lip tissues must grow into contact during the early facial window.	Distance is a developmental variable.
DEV05-E2	The maxillary prominence meets the medial nasal region at the lip boundary.	The contact must occur at the correct neighbor.
DEV05-E3	The joined surface must remodel into continuous tissue.	Touching alone is not the completed lip.

Decision in this update: Choose the label that fits the animation and cite the boundary evidence.

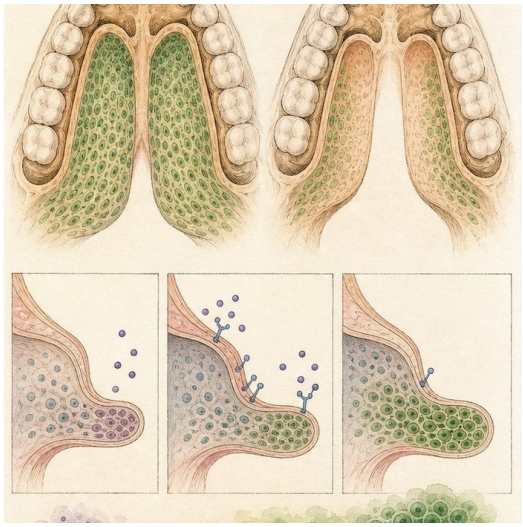
Claim ceiling: You may identify the failed morphologic sequence. You may not identify a gene from the animation alone.

Handoff to the next update: The upper lip closes at about weeks 4 to 6, forming the lip and the small front triangle of palate. But that triangle is only the front of the roof of the mouth. Behind the incisive foramen, the palate is still wide open. So the next question is: how does the palate begin? We chase that next time.

EVIDENCE UPDATE 6 OF 20 | EMBRYOLOGIST

How the Palate Begins: Secondary Palatal Shelf Outgrowth

The secondary palate begins as paired shelves whose cell growth must create enough tissue to reach the midline.



Biomedical teaching illustration: Connect cell proliferation to palatal shelf length

ID	Finding supplied in the case	Why it matters
DEV06-E1	Secondary palatal shelves grow from the inner sides of the maxillary regions.	The palate begins as paired outgrowths.
DEV06-E2	Reduced mesenchymal proliferation can leave shelves too small to meet.	Cell number and shelf size are connected.
DEV06-E3	Directed Bmp4 expression rescued palatal growth and fusion in an Msx1-deficient mouse model.	The experiment supports a growth mechanism in that model.

Decision in this update: Choose the primary outcome and cite the evidence linking cell growth to shelf size.

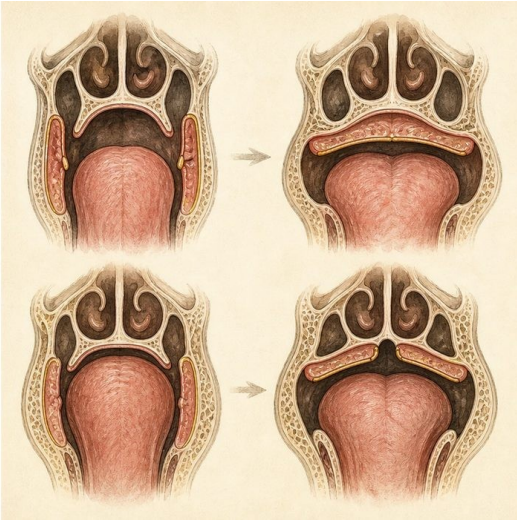
Claim ceiling: You may test a growth mechanism in the model. You may not claim a proven human treatment.

Handoff to the next update: The palate begins as two shelves that grow downward beside the tongue. But those shelves point straight down, with the tongue sitting between them. How do two downward shelves end up as one flat roof above the tongue? We chase that next time.

EVIDENCE UPDATE 7 OF 20 | DEVELOPMENTAL BIOLOGIST

Getting Above the Tongue: Palatal Shelf Elevation

Palatal shelves must rapidly elevate above the tongue, and jaw-tongue geometry can block that movement.



Biomedical teaching illustration: Use jaw and tongue position to explain shelf elevation

ID	Finding supplied in the case	Why it matters
DEV07-E1	Palatal shelves first grow vertically beside the tongue.	Their early position is not the final roof position.
DEV07-E2	The shelves elevate to a horizontal position above the tongue.	Movement is required before midline contact.
DEV07-E3	A small jaw can keep the tongue high and mechanically block elevation.	Geometry can cause cleft palate even when shelves exist.

Decision in this update: Choose the comparison and cite the evidence that separates presence from position.

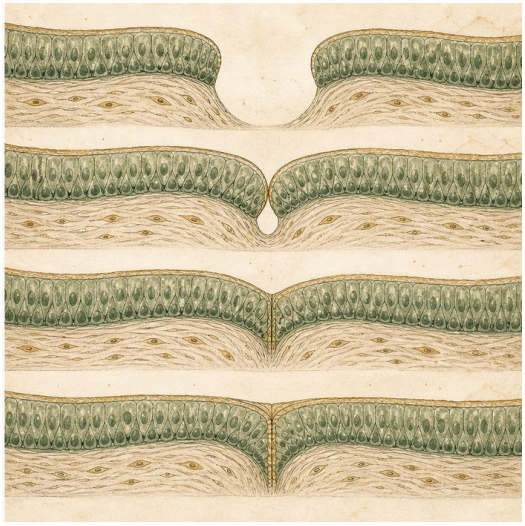
Claim ceiling: You may identify a mechanical elevation problem. You may not assign a syndrome without the full clinical pattern.

Handoff to the next update: The shelves remodel and rise above the tongue once the tongue drops and the head widens. But now the two horizontal shelves sit almost edge to edge at the midline, still separate. What actually lets two separate edges of tissue become one continuous roof? We chase that next time.

EVIDENCE UPDATE 8 OF 20 | HISTOLOGIST

Two Shelves Become One Roof: Adhesion, the Medial Edge Epithelium, and the Seam

After elevation, the medial edges must recognize, adhere to, and align with one another before fusion can continue.



Biomedical teaching illustration: Zoom in on the medial edge epithelium

ID	Finding supplied in the case	Why it matters
DEV08-E1	Elevated shelves grow toward one another at the midline.	Correct position creates the opportunity for contact.
DEV08-E2	The medial edge epithelia make contact and adhere.	A specific surface interaction begins fusion.
DEV08-E3	Contact creates a midline epithelial seam.	The first joined state still contains an epithelial wall.

Decision in this update: Choose the scoring rule and cite the evidence that separates contact from adhesion.

Claim ceiling: You may score contact and adhesion. You may not call mesenchymal fusion complete while the seam remains.

Handoff to the next update: The shelves adhere at their medial edges and form one seam down the midline. But the roof is not truly finished: a wall of epithelial cells, the seam, still runs through it. If that wall stays, the two sides are not really one piece. What happens to that wall of cells? We chase that next time, and the answer turns out to be a real scientific argument.

EVIDENCE UPDATE 9 OF 20 | CELL BIOLOGIST

What Happens to the Wall Between the Shelves: Seam Removal, EMT versus Apoptosis

True palatal fusion requires removal of the midline epithelial seam so mesenchyme becomes continuous.

Biomedical teaching illustration: Test what happens to midline seam cells

ID	Finding supplied in the case	Why it matters
DEV09-E1	A midline epithelial seam forms after the shelves adhere.	The seam is a normal temporary stage.
DEV09-E2	Seam cells are removed through processes that include apoptosis and extrusion.	Cell loss helps eliminate the barrier.
DEV09-E3	Lineage labeling tests whether seam cells remain, move, or change identity.	Mechanism requires tracking, not appearance alone.

Decision in this update: Choose the experiment and explain why the endpoint image is not enough.

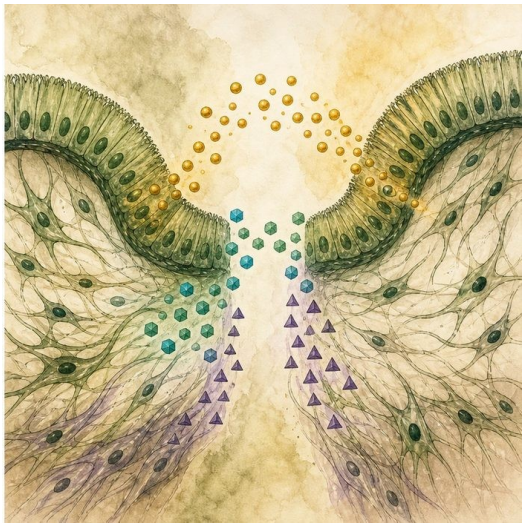
Claim ceiling: You may distinguish supported cell-removal mechanisms. You may not force all seam loss into one mechanism without tracking evidence.

Handoff to the next update: The seam is removed, by mechanisms scientists are still working out, so the palate becomes one continuous tissue. But the seam cells clear at exactly the right time and place, and the shelves grew the right amount and stuck only where they should. Something must be telling the tissue when and where to grow, stick, and clear. What is that signal, and where does it come from? We chase that next time.

EVIDENCE UPDATE 10 OF 20 | MOLECULAR EMBRYOLOGIST

What Tells Tissues When and Where to Grow: The Signaling Centers SHH, BMP, FGF

Signals such as SHH, BMP, and FGF carry local instructions that coordinate growth, position, and cell fate.



Biomedical teaching illustration: Map epithelial-mesenchymal cross-talk

ID	Finding supplied in the case	Why it matters
DEV10-E1	SHH is produced in palatal epithelium and influences nearby mesenchyme.	Signal source and target can be different tissues.
DEV10-E2	BMP and FGF pathways help regulate shelf growth and regional identity.	Several pathways coordinate the process.
DEV10-E3	Changing a pathway in a model can alter proliferation or shape in specific shelf regions.	Signal effects depend on place and time.

Decision in this update: Choose the bounded conclusion and cite source-target and growth evidence.

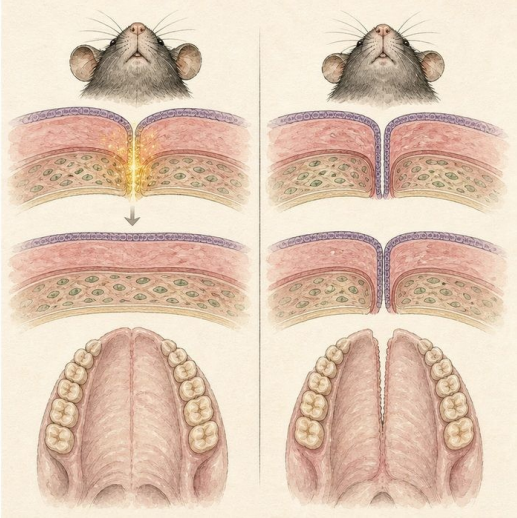
Claim ceiling: You may infer a pathway role in the model and tissue tested. You may not erase other pathways or transfer exposure to Mateo.

Handoff to the next update: SHH, BMP, and FGF tell the shelves how much to grow and where, and a missing signal gives a too-small or mis-grown shelf. But growing is not the same as joining: a shelf can grow, elevate, and meet its partner and STILL not fuse. At the last step the two touching shelves must commit to becoming one, and a specific signal flips that switch. What is the master switch for palate fusion? We chase that next time.

EVIDENCE UPDATE 11 OF 20 | MOLECULAR EMBRYOLOGIST

TGF-beta3, the Fusion Switch in the Medial Edge Epithelium

TGF-beta3 makes the palatal medial edge competent to complete adhesion and seam removal.



Biomedical teaching illustration: Read the Tgfb3 knockout result step by step

ID	Finding supplied in the case	Why it matters
DEV11-E1	In Tgfb3-null mouse embryos, palatal shelves can reach the midline.	Earlier growth and elevation can still occur.
DEV11-E2	The shelves fail to complete normal adhesion and seam removal.	The defect is concentrated at the fusion transition.
DEV11-E3	The result is cleft secondary palate in the model.	Failure of a late step can preserve a gap despite shelf contact.

Decision in this update: Choose the step assignment and cite the matched contact evidence.

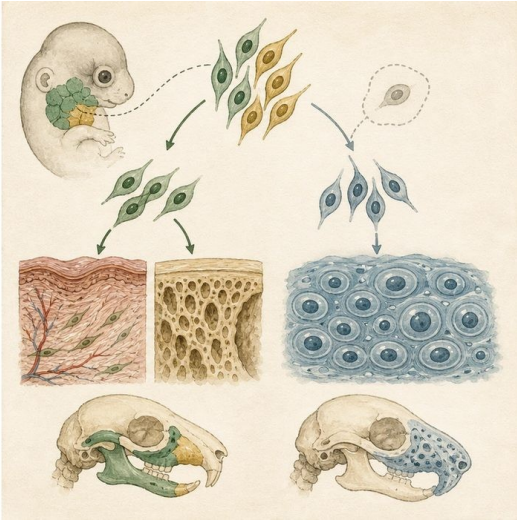
Claim ceiling: You may assign a required role in mouse palatal fusion. You may not claim every human cleft palate is caused by TGFB3.

Handoff to the next update: We found the switch that tells edge cells to fuse. But before any cell can be an edge cell, it first had to BECOME a particular kind of cell. How does a face cell decide whether to be bone, skin, or cartilage in the first place?

EVIDENCE UPDATE 12 OF 20 | DEVELOPMENTAL BIOLOGIST (ATIT LAB COLLABORATION)

The Wnt/beta-catenin Master Switch, How a Face Cell Decides What NOT to Be

Wnt-beta-catenin signaling can steer cranial progenitors toward dermal and bone fates while repressing cartilage fate.



Biomedical teaching illustration: Map the Atit Lab beta-catenin experiment

ID	Finding supplied in the case	Why it matters
DEV12-E1	Control cranial progenitors process Wnt-beta-catenin signaling during fate selection.	The pathway is active during the decision window.
DEV12-E2	Conditional beta-catenin loss removes cranial dermis and bone in the tested region.	The pathway is required for those fates in that model.
DEV12-E3	Lineage-labeled mutant cells form cartilage in their place.	The same progenitor population changed fate rather than simply disappearing.

Decision in this update: Choose the strongest response and cite the evidence that rules against simple cell loss.

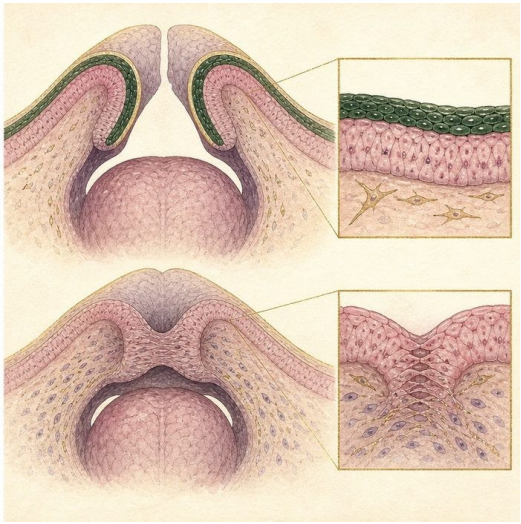
Claim ceiling: You may support an instructive Wnt role in the tested cranial lineage. You may not generalize to every tissue or developmental stage.

Handoff to the next update: We now see how cells choose their fate. But fusion happens at surfaces, and surfaces are dangerous: a sticky outer layer could glue the palate to the tongue by accident. So why do not the wrong surfaces stick together?

EVIDENCE UPDATE 13 OF 20 | CELL BIOLOGIST (EPITHELIAL TEAM, GENETICS OVERLAP)

Periderm and IRF6, the Non-Stick Coating on the Embryo

IRF6-dependent periderm acts as a temporary non-stick surface that prevents the wrong oral tissues from adhering.



Biomedical teaching illustration: Connect IRF6, periderm, and oral adhesion

ID	Finding supplied in the case	Why it matters
DEV13-E1	Periderm covers embryonic oral epithelial surfaces during key stages.	It provides a temporary specialized surface.
DEV13-E2	Irf6-deficient mouse embryos have abnormal periderm differentiation.	IRF6 is required for normal protection in the model.
DEV13-E3	Abnormal oral adhesions can block palatal shelf elevation.	A surface defect can create a later movement defect.

Decision in this update: Choose the causal sequence and cite the surface and movement evidence.

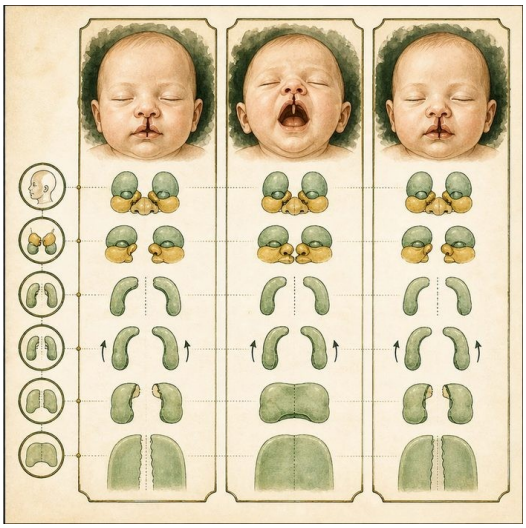
Claim ceiling: You may explain the knockout mechanism. You may not treat all human IRF6 variants as identical to a complete mouse knockout.

Handoff to the next update: We now know which surfaces must stay apart and which must fuse, and which gene polices that. But clefts come in different forms: some only the lip, some only the palate, some both. Which exact step fails for a cleft lip versus a cleft palate?

EVIDENCE UPDATE 14 OF 20 | DEVELOPMENTAL BIOLOGIST (FAILURE-POINT MAPPER)

Mapping the Failure, Which Step Breaks for a Cleft Lip Versus a Cleft Palate

A cleft pattern narrows the failed developmental checkpoint, but it rarely identifies one unique cause.



Biomedical teaching illustration: Read three cleft patterns backward

ID	Finding supplied in the case	Why it matters
DEV14-E1	Cleft lip points to an early upper-lip growth and fusion boundary.	The phenotype localizes an early facial checkpoint.
DEV14-E2	Cleft palate can result from failed shelf growth, elevation, adhesion, or seam removal.	Several mechanisms share the palate endpoint.
DEV14-E3	Mateo has both cleft lip and palate.	His pattern spans connected but distinguishable developmental events.

Decision in this update: Choose the triage method and explain why the palate list remains broader.

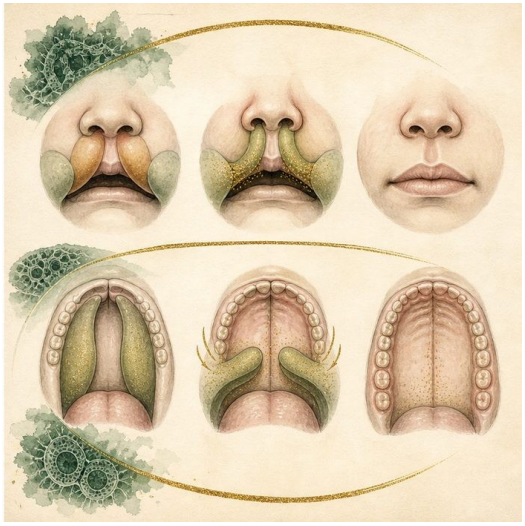
Claim ceiling: You may narrow checkpoints from anatomy. You may not assign one unique molecular cause from phenotype alone.

Handoff to the next update: We can now map which step failed and see that Mateo's looks like an isolated fusion failure. But mapping a failure is not fixing it. Each step happens in a narrow calendar window. Is there a moment after which the step can no longer be repaired, so the cleft becomes locked in?

EVIDENCE UPDATE 15 OF 20 | EMBRYOLOGIST (TIMING SPECIALIST)

Critical Timing Windows, When the Door Closes

A developmental risk matters most when it acts during the short window for the process it can disrupt.



Biomedical teaching illustration: Compare lip and palate critical windows

ID	Finding supplied in the case	Why it matters
DEV15-E1	Upper-lip fusion occurs earlier than completion of secondary-palate fusion.	The two structures have different timing windows.
DEV15-E2	A disruption must overlap a sensitive process to affect that process directly.	Exposure timing is part of causal reasoning.
DEV15-E3	After a cleft is established in utero, later normal growth does not automatically fuse the gap.	Subsequent development builds around the open structure.

Decision in this update: Choose the timing hypothesis and cite the window evidence.

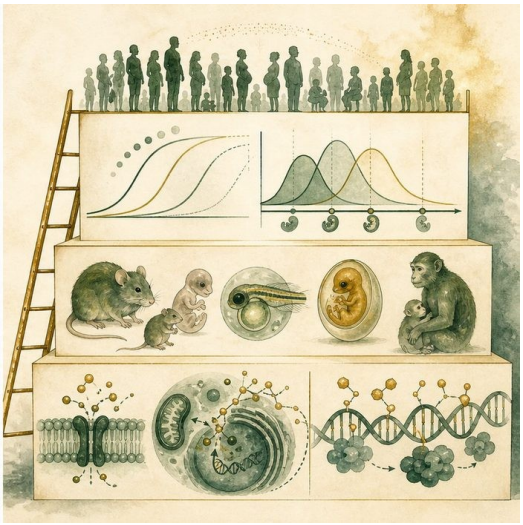
Claim ceiling: You may judge timing compatibility. You may not prove causation from timing alone.

Handoff to the next update: We now know the face has narrow closure windows, and those windows are when it is most fragile. If the embryo is most vulnerable during these weeks, can something from outside the embryo reach in during the window and change whether the face forms correctly?

EVIDENCE UPDATE 16 OF 20 | TERATOLOGY LIAISON

When the Outside World Reaches the Embryo

An environmental factor changes risk only when evidence links dose, timing, and mechanism, and risk is not destiny.



Biomedical teaching illustration: Grade evidence for folate, valproate, and other exposures

ID	Finding supplied in the case	Why it matters
DEV16-E1	Some prenatal exposures are associated with higher cleft risk in populations.	Association can identify a factor worth studying.
DEV16-E2	Valproate is a known teratogenic medication whose risks depend on exposure context and timing.	A specific factor can have biologically important prenatal effects.
DEV16-E3	Most exposed pregnancies do not produce the same outcome, and many clefts occur without a known exposure.	Risk is probabilistic and multifactorial.

Decision in this update: Choose the explanation and cite evidence about probability and case limits.

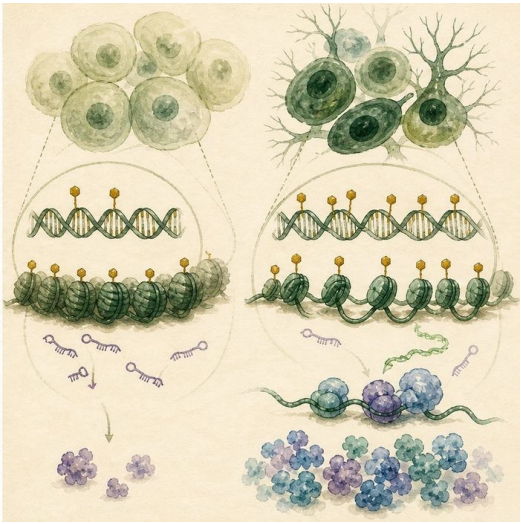
Claim ceiling: You may explain population risk and biological plausibility. You may not assign an unrecorded exposure or blame.

Handoff to the next update: Yes, the environment can tip the odds during the fusion window. But here is the puzzle: the same exposure can reach two embryos with the same DNA and only one of them clefts. How can identical DNA give different results?

EVIDENCE UPDATE 17 OF 20 | EPIGENETICIST

Same DNA, Different Outcome

The same DNA can produce different outcomes because gene activity and developmental context can differ.



Biomedical teaching illustration: Separate DNA sequence from epigenetic regulation

ID	Finding supplied in the case	Why it matters
DEV17-E1	DNA methylation can change gene activity without changing the DNA letters.	Sequence and regulation are separate layers.
DEV17-E2	MicroRNAs can reduce how much protein is made from target messages.	Post-transcriptional regulation can alter pathway output.
DEV17-E3	Cleft penetrance can vary among people with similar genetic susceptibility.	A susceptibility variant does not force one outcome.

Decision in this update: Choose the testable explanation and cite sequence-versus-regulation evidence.

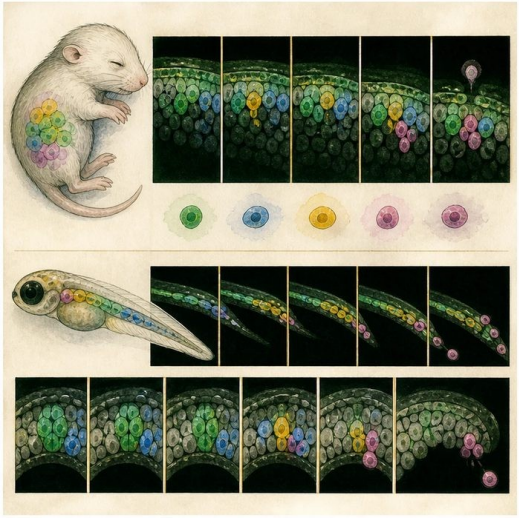
Claim ceiling: You may propose an epigenetic modifier. You may not convert an association into a single proven cause.

Handoff to the next update: Epigenetic marks and tiny RNAs let identical DNA give different outcomes, and isolated clefting behaves like an additive, multifactorial trait. But we just reasoned from human DNA, mouse palates, and zebrafish cartilage at once. How do scientists actually watch development happen?

EVIDENCE UPDATE 18 OF 20 | COMPARATIVE EMBRYOLOGIST

Watching Development Happen

Researchers combine lineage labels, live imaging, and model organisms to turn hidden developmental events into visible evidence.



Biomedical teaching illustration: Choose a method to watch development

ID	Finding supplied in the case	Why it matters
DEV18-E1	Lineage labels mark a cell population and its descendants.	They answer where cells came from and what they became.
DEV18-E2	Live imaging records movement and cell behavior over time.	It can reveal order and timing.
DEV18-E3	Mouse and zebrafish models share important developmental mechanisms but are not identical to humans.	Model choice sets a limit on transfer.

Decision in this update: Choose the method set and cite the evidence for both time and identity.

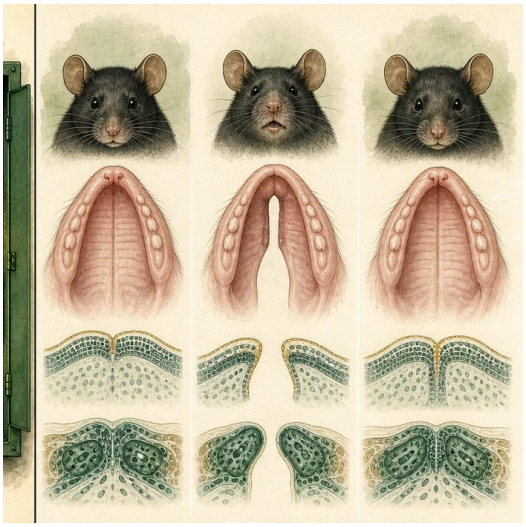
Claim ceiling: You may observe mechanism in the selected model. You may not assume every human embryo follows every model detail.

Handoff to the next update: Model organisms plus live imaging let us watch each step of fusion and pin down which one failed. So a bold question: if we can see exactly which step fails and exactly when, could a scientist step in during the window and prevent a cleft?

EVIDENCE UPDATE 19 OF 20 | DEVELOPMENTAL BIOLOGIST (RESCUE STRATEGIST)

If We Know the Window and the Signal, Could We Prevent a Cleft?

A rescue experiment supports a mechanism when restoring one step restores the outcome, but it is not yet a human treatment.



Biomedical teaching illustration: Interpret the Msx1-Bmp4 mouse rescue

ID	Finding supplied in the case	Why it matters
DEV19-E1	Msx1-deficient mice show reduced anterior palatal growth and cleft palate.	The mutant provides a defined disrupted pathway.
DEV19-E2	Directed Bmp4 expression restored growth and fusion in the reported mouse model.	Restoring a downstream signal rescued the phenotype.
DEV19-E3	The intervention was genetic and preclinical in mice.	The experiment is not a tested prenatal therapy for humans.

Decision in this update: Choose the accurate headline and cite both the rescue and translation-limit evidence.

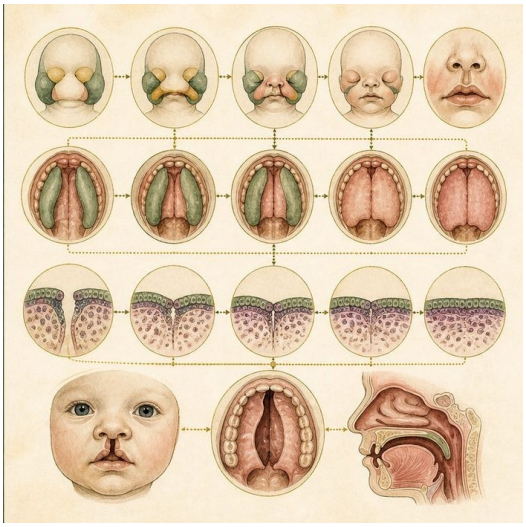
Claim ceiling: You may state proof of mechanism in the model. You may not claim safety, timing, delivery, or effectiveness in humans.

Handoff to the next update: We can rescue a cleft in a mouse by adding back one signal, but only in the lab and only by editing the embryo's own genes. So we still owe Mateo one thing: the complete, honest developmental story of how his cleft actually happened, assembled from everything we learned.

EVIDENCE UPDATE 20 OF 20 | WHOLE DEVELOPMENTAL TEAM (SYNTHESIS)

Mateo's Complete Developmental Story

Mateo's cleft is best explained as a developmental pathway outcome with bounded evidence, not as one proven cause.



Biomedical teaching illustration: Assemble Mateo's complete developmental story

ID	Finding supplied in the case	Why it matters
DEV20-E1	Mateo has complete unilateral left cleft lip and palate with no broader anomaly pattern established in the composite file.	The phenotype is specific while the cause remains open.
DEV20-E2	Lip and palate formation require ordered growth, cell movement, signaling, adhesion, and seam removal.	Several developmental checkpoints can contribute to the final pattern.
DEV20-E3	The case file does not establish one causal variant, exposure, or syndrome.	The final explanation must remain multifactorial and bounded.

Decision in this update: Choose the summary and cite the phenotype evidence plus the uncertainty evidence.

Claim ceiling: You may synthesize the supported developmental pathway. You may not add a diagnosis, variant, or exposure absent from the case file.

Handoff to the next update: Mateo's cleft is an isolated, multifactorial failure of fusion in the weeks 4 to 12 window, with the rest of development normal. The developmental team now hands his fusion-failure story to the genetics, anatomical, and clinical teams. Do their stories agree with ours?