Teach the Evidence Chain

Each lesson moves from analogy to biology to a bounded clinical decision.

Standard 45-minute lesson flow

Minutes	Teacher and student move
0-5	Carry forward the prior take-home and state today's question.
5-12	Show only the analogy panel. Ask the three observation questions.
12-18	Students write the three rules. Name where the analogy stops.
18-27	Reveal the biomedical panel. Map each rule onto the case.
27-38	Students read labeled evidence and make the concrete decision.
38-45	Reveal the strongest answer, write CER, and state the next unlock.

TEACHER PLAN 1 OF 20 | INTAKE GENETICIST

Chance or Genetic? Reading Mateo's Family Tree

Students will read and build a three-generation pedigree using standard symbols and use it to tell an isolated cleft from a familial (inherited) one when the family history…

CARRY FORWARD

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

10-YEAR TAKEAWAY

A pedigree shows how a trait travels through a family; it does not prove that an isolated case is non-genetic.

Socratic launch

Show the analogy panel only: A neighborhood map shows connections, not hidden wiring. Do not name the biology yet.

- Which connections can the map show directly?
- What important system remains hidden underground?
- Why would one affected home not prove a random event?

Rules students should earn

- Record relationships before explaining cause.
- An absent family pattern lowers some hypotheses but does not erase genetics.
- One pedigree is evidence, not a final mechanism.

Biology reveal and evidence

ID	Finding supplied in the case
GEN01-E1	Mateo is the only reported relative with a cleft across three generations.
GEN01-E2	Both parents are unaffected.
GEN01-E3	Isolated clefts can still involve inherited and new genetic risk factors.

Decision and answer guidance

Situation: Mateo's parents ask whether the empty family history means the cleft was only chance.

Strongest option: Say the pedigree looks isolated but cannot exclude genetic risk.

Evidence required: GEN01-E1 + GEN01-E2

Claim ceiling: You may describe the observed family pattern. You may not exclude genetic contribution or name an inheritance model yet.

Next handoff: Mateo's cleft looks isolated and his parents are unaffected, but a cleft can sometimes be one feature of a hidden syndrome. What would a…

TEACHER PLAN 2 OF 20 | CLINICAL GENETICIST

Screening for a Hidden Syndrome

Students will triage a cleft by its associated features, use lower-lip pits to recognize Van der Woude syndrome, and apply that screen to decide that Mateo's cleft looks…

CARRY FORWARD

A pedigree shows how a trait travels through a family; it does not prove that an isolated case is non-genetic.

10-YEAR TAKEAWAY

A syndrome claim requires a repeatable pattern of features, not a cleft plus a familiar gene name.

Socratic launch

Show the analogy panel only: One instrument or the whole musical theme. Do not name the biology yet.

- What turns one sound into a repeated theme?
- Which repeated features would make a pattern recognizable?
- Why is one shared note not enough?

Rules students should earn

- Screen for a set of associated features.
- Use both present and absent findings.
- A gene name does not replace phenotype evidence.

Biology reveal and evidence

ID	Finding supplied in the case
GEN02-E1	Mateo has no lower-lip pits on repeated examination.
GEN02-E2	No additional anomaly pattern or affected relative is documented.
GEN02-E3	IRF6-related disorders are established by suggestive findings plus a pathogenic IRF6 variant.

Decision and answer guidance

Situation: A teammate wants to label Van der Woude syndrome because IRF6 will be studied later.

Strongest option: Keep the case isolated-appearing pending molecular evidence.

Evidence required: GEN02-E1 + GEN02-E2

Claim ceiling: You may say the current screen is isolated-appearing. You may not establish or exclude every syndrome without appropriate testing.

Next handoff: Mateo has no lip pits and no other features, so his cleft screens as isolated. But even an isolated cleft must follow some inheritance…

TEACHER PLAN 3 OF 20 | CLINICAL GENETICIST

Does It Run in Families Like a Single Gene?

Students will compare clean autosomal dominant inheritance against the multifactorial threshold model and use Mateo's sparse, non-vertical pedigree to argue that his isolated cleft fits the multifactorial picture…

CARRY FORWARD

A syndrome claim requires a repeatable pattern of features, not a cleft plus a familiar gene name.

10-YEAR TAKEAWAY

Most isolated clefts fit a multifactorial threshold model in which many small influences add to risk.

Socratic launch

Show the analogy panel only: Several weights tip a balanced scale. Do not name the biology yet.

- Can one small weight tip the scale by itself?
- Why might two people carry different combinations?
- What changes when the total crosses the line?

Rules students should earn

- Add multiple small contributions.
- Risk and outcome are not the same thing.
- Crossing a threshold can produce a yes-or-no anatomy from graded liability.

Biology reveal and evidence

ID	Finding supplied in the case
GEN03-E1	Mateo's pedigree does not show clean vertical transmission.
GEN03-E2	Isolated cleft risk is influenced by many genetic loci and non-genetic factors.
GEN03-E3	A person can carry risk factors without developing a cleft.

Decision and answer guidance

Situation: The board offers either one dominant allele with complete penetrance or a multifactorial threshold model.

Strongest option: Choose the multifactorial threshold model.

Evidence required: GEN03-E1 + GEN03-E2

Claim ceiling: You may choose the best-fit model. You may not calculate Mateo's exact liability or identify each contributor.

Next handoff: Mateo's cleft fits a multifactorial model where many small factors add up. But to understand cleft biology at all, scientists study the best-understood cleft…

Hunting the Exemplar Cleft Gene: Linkage to 1q32

Students will use linkage and co-segregation of DNA markers in informative families to narrow an unknown gene to a chromosomal region (1q32), and understand why scientists use clean…

CARRY FORWARD

Most isolated clefts fit a multifactorial threshold model in which many small influences add to risk.

10-YEAR TAKEAWAY

Linkage follows inherited chromosome markers to narrow a gene's address before sequencing names the gene.

Socratic launch

Show the analogy panel only: Track a delivery truck by the landmarks it passes. Do not name the biology yet.

- Which landmark stays with the truck most often?
- What would a route change separate?
- How close must a landmark be to remain useful?

Rules students should earn

- Track co-inheritance across relatives.
- Recombination can separate distant markers.
- Strong linkage narrows a region, not one final gene.

Biology reveal and evidence

ID	Finding supplied in the case
GEN04-E1	In large Van der Woude families, certain chromosome 1 markers co-segregated with the phenotype.
GEN04-E2	Recombination events narrowed the shared interval to 1q32.
GEN04-E3	The interval still contained more than one possible gene.

Decision and answer guidance

Situation: A marker travels with the syndrome in nearly every informative relative, but several genes lie nearby.

Strongest option: Prioritize the linked interval for sequencing.

Evidence required: GEN04-E1 + GEN04-E2

Claim ceiling: You may prioritize a locus. You may not call a marker causal or name IRF6 before sequence evidence.

Next handoff: We have an address, chromosome 1q32, but an address is not a name. What is the actual gene sitting there, and what does it…

The Gene at 1q32 Has a Name: IRF6, From DNA to Protein

Students will trace a gene from DNA to mRNA to protein (transcription and translation) and identify IRF6 as the gene at 1q32 that makes the IRF6 protein, a…

CARRY FORWARD

Linkage follows inherited chromosome markers to narrow a gene's address before sequencing names the gene.

10-YEAR TAKEAWAY

IRF6 encodes a transcription factor that changes cell behavior by controlling other genes.

Socratic launch

Show the analogy panel only: A recipe card becomes a kitchen supervisor. Do not name the biology yet.

- Which object stores the lasting instructions?
- What copy leaves the archive?
- How can one supervisor change many stations?

Rules students should earn

- DNA is transcribed into an RNA copy.
- RNA is translated into protein.
- A transcription factor regulates other genes rather than building tissue directly.

Biology reveal and evidence

ID	Finding supplied in the case
GEN05-E1	Sequencing the linked 1q32 interval identified damaging variants in IRF6.
GEN05-E2	IRF6 is transcribed into mRNA and translated into a 467-amino-acid protein.
GEN05-E3	IRF6 contains a DNA-binding domain and regulates epithelial differentiation genes.

Decision and answer guidance

Situation: A new intern says IRF6 is a piece of lip tissue made directly from DNA.

Strongest option: Correct the path to DNA, RNA, transcription factor, target genes, and cell behavior.

Evidence required: GEN05-E1 + GEN05-E2

Claim ceiling: You may describe IRF6's molecular role. You may not say one IRF6 result explains Mateo without a case test.

Next handoff: Now that we have the exemplar gene IRF6, where do we look up whether a given variant in it is already known, and whether…

Looking Up a Variant

Students will navigate ClinVar and OMIM and classify a variant entry as benign, pathogenic, or a variant of uncertain significance (VUS).

CARRY FORWARD

IRF6 encodes a transcription factor that changes cell behavior by controlling other genes.

10-YEAR TAKEAWAY

Variant interpretation combines clinical assertions, population frequency, molecular consequence, and evidence quality.

Socratic launch

Show the analogy panel only: A library catalog card needs several trust signals. Do not name the biology yet.

- Which card has the strongest review trail?
- Why does a rare book not have to be harmful?
- What should happen when reviewers disagree?

Rules students should earn

- Read classification with review status.
- Check population frequency and condition match.
- Treat uncertain and conflicting evidence honestly.

Biology reveal and evidence

ID	Finding supplied in the case
GEN06-E1	ClinVar stores submitted variant-condition classifications and review status.
GEN06-E2	A pathogenic IRF6 assertion should match an IRF6-related condition and supporting evidence.
GEN06-E3	A common population variant is unlikely to cause a rare fully penetrant syndrome by itself.

Decision and answer guidance

Situation: An IRF6 record says pathogenic but has one old submission and no assertion criteria; another lab calls it uncertain.

Strongest option: Report the conflict and seek stronger current evidence.

Evidence required: GEN06-E1 + GEN06-E2

Claim ceiling: You may summarize database evidence. You may not independently diagnose from a weak or conflicting record.

Next handoff: When we read variants we saw codes like R84C and R250X. What kinds of typos in DNA do those codes actually stand for?

TEACHER PLAN 7 OF 20 | VARIANT ANALYST

Kinds of Typos in DNA

Students will classify a DNA change as missense, nonsense, frameshift, or splice from a sequence and predict its effect on the protein.

CARRY FORWARD

Variant interpretation combines clinical assertions, population frequency, molecular consequence, and evidence quality.

10-YEAR TAKEAWAY

DNA variants change proteins in different ways, so variant type is evidence about mechanism, not a verdict by itself.

Socratic launch

Show the analogy panel only: Edit one instruction manual four different ways. Do not name the biology yet.

- Which edit changes one item but keeps the rest?
- Which edit stops the message early?
- Which edit shifts every group after it?

Rules students should earn

- Missense swaps one amino acid.
- Nonsense and frameshift variants can truncate protein.
- Splice variants can change which RNA sections remain.

Biology reveal and evidence

ID	Finding supplied in the case
GEN07-E1	A missense variant replaces one amino acid.
GEN07-E2	A nonsense or frameshift variant can create a premature stop.
GEN07-E3	A splice-site variant can alter exon joining.

Decision and answer guidance

Situation: Report A is missense, B is an early nonsense, and C is a splice-site change near an exon boundary.

Strongest option: Predict different possible consequences and request location-specific evidence.

Evidence required: GEN07-E1 + GEN07-E2

Claim ceiling: You may predict molecular consequences. You may not classify pathogenicity from variant type alone.

Next handoff: We can sort IRF6 typos by type. But IRF6 causes two different diseases, a milder one and a more severe one. Why would one…

TEACHER PLAN 8 OF 20 | VARIANT ANALYST

One Gene, Two Diseases

Students will connect mutation mechanism to phenotype, contrasting haploinsufficiency (truncating, milder Van der Woude) with dominant-negative action (DNA-binding-domain missense, more severe popliteal pterygium).

CARRY FORWARD

DNA variants change proteins in different ways, so variant type is evidence about mechanism, not a verdict by itself.

10-YEAR TAKEAWAY

Variant location can change mechanism: reduced dosage and altered DNA binding can produce different IRF6-related outcomes.

Socratic launch

Show the analogy panel only: A two-person control room can fail in two ways. Do not name the biology yet.

- What happens when one station is empty?
- How is a wrong command different from no command?
- Which failure could disrupt the working operator too?

Rules students should earn

- One missing functional copy can reduce dosage.
- A changed protein can interfere with normal complexes.
- Domain location helps predict the mechanism.

Biology reveal and evidence

ID	Finding supplied in the case
GEN08-E1	Many Van der Woude variants reduce the amount of functional IRF6.
GEN08-E2	Some severe PPS-associated variants cluster at Arg84 in the DNA-binding domain.
GEN08-E3	Different substitutions at Arg84 do not always produce the same phenotype.

Decision and answer guidance

Situation: One creates an early stop. The other changes Arg84 in the DNA-binding domain.

Strongest option: Discuss dosage loss versus domain-specific altered function.

Evidence required: GEN08-E1 + GEN08-E2

Claim ceiling: You may compare supported mechanisms. You may not guarantee syndrome severity from variant position alone.

Next handoff: The harmful IRF6 changes we studied are rare and cause syndromes. Most clefts are isolated and common. Where is the common, hidden variant, and…

TEACHER PLAN 9 OF 20 | VARIANT ANALYST

The Hidden Regulatory Variant

Students will distinguish coding from regulatory variants and explain how the common nonsyndromic cleft-lip risk variant rs642961 raises risk by disrupting an AP-2alpha enhancer instead of changing the…

CARRY FORWARD

Variant location can change mechanism: reduced dosage and altered DNA binding can produce different IRF6-related outcomes.

10-YEAR TAKEAWAY

A regulatory variant changes when or how much a gene is used without changing the protein sequence.

Socratic launch

Show the analogy panel only: The machine is intact, but its dimmer switch changes output. Do not name the biology yet.

- What stays identical in both machines?
- Which control changes the amount produced?
- Why would output depend on the room and time?

Rules students should earn

- Coding sequence and regulation are separate.
- Enhancers control context-specific expression.
- A risk allele changes probability rather than guaranteeing disease.

Biology reveal and evidence

ID	Finding supplied in the case
GEN09-E1	rs642961 lies in an IRF6 enhancer rather than a protein-coding exon.
GEN09-E2	The risk allele disrupts an AP-2alpha binding site in laboratory assays.
GEN09-E3	The allele is associated with increased cleft-lip risk but is found in unaffected people.

Decision and answer guidance

Situation: A report finds one rs642961 risk allele and no pathogenic coding variant.

Strongest option: Describe a modest regulatory risk contribution, not a diagnosis.

Evidence required: GEN09-E1 + GEN09-E2

Claim ceiling: You may describe association and mechanism. You may not claim the allele alone caused Mateo's cleft.

Next handoff: A regulatory variant lowers how MUCH IRF6 is made, while syndromic variants damage specific protein parts. To understand both, we need to see the…

What the IRF6 Protein Looks Like

Students will describe the IRF6 protein's two-domain architecture (a DNA-binding domain and a protein-binding SMIR/IAD domain) and explain why a variant's domain location predicts its effect.

CARRY FORWARD

A regulatory variant changes when or how much a gene is used without changing the protein sequence.

10-YEAR TAKEAWAY

Protein domains are specialized working regions, so a variant's position helps predict which function may fail.

Socratic launch

Show the analogy panel only: A multi-tool has separate working sections. Do not name the biology yet.

- Which part performs each job?
- Would damage to the handle equal damage to the gripping tip?
- Why map a defect before testing function?

Rules students should earn

- Proteins contain functional domains.
- Domain position narrows the likely disrupted job.
- Unstructured regions can still matter even when less conserved.

Biology reveal and evidence

ID	Finding supplied in the case
GEN10-E1	IRF6 is 467 amino acids long.
GEN10-E2	The N-terminal DNA-binding domain spans roughly residues 7 to 115.
GEN10-E3	The C-terminal SMIR/IAD region supports protein interactions.

Decision and answer guidance

Situation: Variant A lies in the DNA-binding domain; variant B lies in the C-terminal interaction region.

Strongest option: Test DNA binding for A and partner interaction for B.

Evidence required: GEN10-E1 + GEN10-E2

Claim ceiling: You may select assays from domain location. You may not classify a variant without results and other evidence.

Next handoff: Our protein has critical domains. How can we tell which parts are so important that evolution never lets them change?

Is This Gene Important Across Species?

Use a multi-species alignment and the logic of conservation to argue which parts of the IRF6 protein are functionally essential, then flag a variant of unknown meaning as…

CARRY FORWARD

Protein domains are specialized working regions, so a variant's position helps predict which function may fail.

10-YEAR TAKEAWAY

Evolutionary conservation marks positions that tolerated little change, adding evidence that a new change may matter.

Socratic launch

Show the analogy panel only: Compare many editions to find the words no editor changes. Do not name the biology yet.

- Which parts remain unchanged across every edition?
- What does repeated preservation suggest?
- Can preservation alone prove a new edit is harmful?

Rules students should earn

- Align orthologous sequences.
- High conservation suggests functional constraint.
- Conservation supports, but does not settle, variant classification.

Biology reveal and evidence

ID	Finding supplied in the case
GEN11-E1	IRF6 orthologs occur across many vertebrate species.
GEN11-E2	The DNA-binding domain has highly conserved residues, including Arg84.
GEN11-E3	Some conserved-position variants have different clinical effects.

Decision and answer guidance

Situation: The residue is identical in five vertebrates, but no patient or functional data exist.

Strongest option: Use conservation as supporting evidence and keep classification uncertain.

Evidence required: GEN11-E1 + GEN11-E2

Claim ceiling: You may say the site is constrained. You may not make conservation the only pathogenicity criterion.

Next handoff: We found that the DNA-binding domain is conserved across species, so it must be essential. But if those exact amino acids are protected across…

How Does One Wrong Amino Acid Break the Protein?

Use an AlphaFold view of the IRF6 DNA-binding domain to connect structure to function, and predict how a single missense change disrupts either DNA binding directly or the…

CARRY FORWARD

Evolutionary conservation marks positions that tolerated little change, adding evidence that a new change may matter.

10-YEAR TAKEAWAY

A missense variant matters when its side-chain change disrupts a specific protein interaction or fold.

Socratic launch

Show the analogy panel only: One replacement key no longer fits the lock. Do not name the biology yet.

- Which tiny shape difference prevents fitting?
- Why might another key change still work?
- What direct test would show loss of grip?

Rules students should earn

- Amino-acid side chains have different size, charge, and chemistry.
- Local structure determines the effect.
- A model predicts; a binding assay tests.

Biology reveal and evidence

ID	Finding supplied in the case
GEN12-E1	Arg84 lies in the conserved IRF6 DNA-binding domain.
GEN12-E2	Replacing arginine changes side-chain chemistry and may alter DNA contact or local folding.
GEN12-E3	AlphaFold predicts structure but does not measure variant function.

Decision and answer guidance

Situation: The model predicts an altered DNA-contact surface, but no binding experiment has been run.

Strongest option: Report a supported hypothesis and request functional testing.

Evidence required: GEN12-E1 + GEN12-E2

Claim ceiling: You may propose a structure-function mechanism. You may not present a prediction as measured protein behavior.

Next handoff: We found that one wrong amino acid in the conserved domain can stop IRF6 from gripping DNA. But a transcription factor never works alone.…

Does IRF6 Work Alone?

Read a gene regulatory network from patient and experimental clues, and place IRF6 in the p63 to IRF6 to GRHL3 axis with KLF4 and KLF17 downstream.

CARRY FORWARD

A missense variant matters when its side-chain change disrupts a specific protein interaction or fold.

10-YEAR TAKEAWAY

IRF6 works in a regulatory network, so similar phenotypes can arise when different connected genes fail.

Socratic launch

Show the analogy panel only: A relay team passes one signal through several runners. Do not name the biology yet.

- Who acts before the middle runner?
- Which handoff could stop the same finish?
- Why would two different failed runners create similar outcomes?

Rules students should earn

- Name upstream and downstream relationships.
- Different nodes can converge on one cell behavior.
- Network redundancy can soften or redirect a failure.

Biology reveal and evidence

ID	Finding supplied in the case
GEN13-E1	p63 and TGF-beta signaling influence IRF6 expression or activity in oral epithelium.
GEN13-E2	IRF6 promotes GRHL3, KLF4, and KLF17-related differentiation programs.
GEN13-E3	GRHL3 variants can also cause Van der Woude-like phenotypes.

Decision and answer guidance

Situation: IRF6 sequencing is negative, but the phenotype remains strongly suggestive of the network.

Strongest option: Consider other connected genes and broader testing.

Evidence required: GEN13-E1 + GEN13-E2

Claim ceiling: You may broaden the candidate network. You may not diagnose a specific second gene without evidence.

Next handoff: We placed IRF6 in a network with p63 above it and GRHL3 and the KLFs alongside and below. But a network of genes is…

What Does IRF6 Actually Do in the Embryo?

Connect the IRF6 gene to a single cell behavior, periderm differentiation, and trace how losing that behavior turns a gene change into a physical cleft.

CARRY FORWARD

IRF6 works in a regulatory network, so similar phenotypes can arise when different connected genes fail.

10-YEAR TAKEAWAY

The IRF6 network helps oral epithelial cells form periderm, preventing wrong adhesions before correct fusion.

Socratic launch

Show the analogy panel only: Temporary release paper protects adhesive surfaces. Do not name the biology yet.

- Why must the protection exist before contact?
- What happens if the wrong surfaces stick first?
- When can the protective layer safely change?

Rules students should earn

- Differentiate a temporary protective surface.
- Prevent wrong adhesion before enabling correct fusion.
- A cell-autonomous defect can create a tissue-level block.

Biology reveal and evidence

ID	Finding supplied in the case
GEN14-E1	IRF6 is active in oral epithelium and periderm differentiation.
GEN14-E2	Irf6-deficient models lose normal periderm and develop abnormal oral adhesions.
GEN14-E3	Those adhesions can block palatal elevation and closure.

Decision and answer guidance

Situation: The board requires one sequence from gene to cell to tissue outcome.

Strongest option: IRF6 network failure, periderm defect, wrong adhesion, blocked closure.

Evidence required: GEN14-E1 + GEN14-E2

Claim ceiling: You may explain an established model mechanism. You may not claim Mateo has IRF6 loss without a result.

Next handoff: We found that IRF6 makes periderm cells differentiate so the shelves can fuse, and without it they stick wrongly and stay open. But a…

How Do We Prove the Gene Causes It?

Use the logic of model-organism knockouts and rescue experiments to argue that IRF6 loss causes clefting rather than merely correlating with it.

CARRY FORWARD

The IRF6 network helps oral epithelial cells form periderm, preventing wrong adhesions before correct fusion.

10-YEAR TAKEAWAY

Knockout and rescue experiments strengthen causation when loss creates a defect and restoration reverses part of it.

Socratic launch

Show the analogy panel only: Remove one bridge cable, then restore it. Do not name the biology yet.

- Which comparison shows necessity?
- Which comparison tests sufficiency or rescue?
- Why might a partial rescue still teach mechanism?

Rules students should earn

- Compare matched control and knockout groups.
- Restore the suspected function in a defined tissue or time.
- Measure both rescue and remaining defects.

Biology reveal and evidence

ID	Finding supplied in the case
GEN15-E1	Irf6 knockout models develop abnormal epithelium, oral adhesions, and cleft palate.
GEN15-E2	Restoring epithelial IRF6 reduces some adhesions but does not fully rescue every defect.
GEN15-E3	Zebrafish rescue experiments add evidence in a second model.

Decision and answer guidance

Situation: The rescue group has fewer adhesions but still has cleft palate in several regions.

Strongest option: Call it a partial mechanistic rescue.

Evidence required: GEN15-E1 + GEN15-E2

Claim ceiling: You may support causation and a tissue role. You may not claim complete rescue or human treatment.

Next handoff: We proved IRF6 loss causes clefting using knockout and rescue in mouse and zebrafish, so we now understand how the cleft happens in one…

Why Is CL/P More Common in Some Groups?

Explain how allele frequency, ancestry, gene-environment interaction, and a liability threshold combine to make CL/P more common in some populations, and why a risk score built in one…

CARRY FORWARD

Knockout and rescue experiments strengthen causation when loss creates a defect and restoration reverses part of it.

10-YEAR TAKEAWAY

Population differences reflect allele frequencies, effect sizes, environments, and sampling, not biological ranking of groups.

Socratic launch

Show the analogy panel only: Different gardens contain different seed mixes and weather. Do not name the biology yet.

- Which factors differ between gardens?
- Why can the same seed behave differently?
- What would replication across gardens test?

Rules students should earn

- Separate ancestry from race labels.
- Compare allele frequency and effect size.
- Require replication and consider environment and sampling.

Biology reveal and evidence

ID	Finding supplied in the case
GEN16-E1	Cleft prevalence differs among studied populations.
GEN16-E2	Risk-allele frequencies and effect estimates can differ by ancestry and study.
GEN16-E3	Within-group variation is large and ancestry groups overlap.

Decision and answer guidance

Situation: The draft says one ancestry group is genetically destined to have more clefts.

Strongest option: Replace it with frequency, context, overlap, and replication language.

Evidence required: GEN16-E1 + GEN16-E2

Claim ceiling: You may discuss population statistics. You may not rank groups biologically or predict an individual from ancestry alone.

Next handoff: We found why CL/P differs across whole populations, but population averages are not a family. Mateo's parents now ask the practical question: if they…

What Is the Family's Recurrence Risk?

Apply Mendelian and multifactorial empiric recurrence-risk figures to estimate the chance of a cleft in a family's next child, and describe the counselor's non-directive ethical role.

CARRY FORWARD

Population differences reflect allele frequencies, effect sizes, environments, and sampling, not biological ranking of groups.

10-YEAR TAKEAWAY

Recurrence counseling uses empiric family data and uncertainty; it gives a range, not a promise.

Socratic launch

Show the analogy panel only: A weather forecast guides planning without guaranteeing rain. Do not name the biology yet.

- How does a forecast help if it is not certain?
- What information changes the forecast?
- How should uncertainty be communicated?

Rules students should earn

- Use the best-matched family and phenotype data.
- State a range and the source of uncertainty.
- Support family autonomy without blame.

Biology reveal and evidence

ID	Finding supplied in the case
GEN17-E1	Mateo's case is isolated-appearing with unaffected parents.
GEN17-E2	Empiric recurrence estimates come from outcomes in similar families.
GEN17-E3	A confirmed pathogenic familial variant would change the counseling model.

Decision and answer guidance

Situation: They ask for one guaranteed percentage before deciding about future pregnancy.

Strongest option: Give a sourced empiric range and explain what could refine it.

Evidence required: GEN17-E1 + GEN17-E2

Claim ceiling: You may provide an educational empiric range from the supplied source. You may not personalize medical advice beyond the composite evidence.

Next handoff: We can now counsel the family honestly about the odds, but giving a number does not change the gene. Sooner or later a family…

TEACHER PLAN 18 OF 20 | GENE THERAPIST

Can We Fix the Code?

Describe three molecular strategies to correct or compensate for a clefting gene defect, and explain clearly that every one is preclinical with no human therapy in use.

CARRY FORWARD

Recurrence counseling uses empiric family data and uncertainty; it gives a range, not a promise.

10-YEAR TAKEAWAY

Gene editing, pathway rescue, and gene-dosage modulation are different strategies with different targets and risks.

Socratic launch

Show the analogy panel only: Repair a program by editing code, changing settings, or adding a patch. Do not name the biology yet.

- Which repair changes the original code?
- Which repair changes output without rewriting?
- Which repair may work only during one window?

Rules students should earn

- Name the molecular target and cell type.
- Separate permanent editing from temporary pathway modulation.
- Require delivery, timing, safety, and off-target evidence.

Biology reveal and evidence

ID	Finding supplied in the case
GEN18-E1	Animal studies have rescued some cleft-related model phenotypes through pathway or gene restoration.
GEN18-E2	The face forms during early, short developmental windows.
GEN18-E3	No established prenatal gene-editing treatment prevents common human cleft lip and palate.

Decision and answer guidance

Situation: The company says animal rescue results mean fetal CRISPR for clefts is clinic-ready.

Strongest option: Reject clinic-ready language and list delivery, timing, safety, and evidence gaps.

Evidence required: GEN18-E1 + GEN18-E2

Claim ceiling: You may compare preclinical strategies. You may not claim an available or proven human prenatal treatment.

Next handoff: These fixes work in animals today, and the science is moving. That raises a question no experiment can answer: if correcting a cleft gene…

TEACHER PLAN 19 OF 20 | BIOETHICIST

Should We, and Who Decides?

Use a structured reasoning model to weigh somatic versus germline editing for clefting against benefit, risk, equity, and consent, and reach a defended position.

CARRY FORWARD

Gene editing, pathway rescue, and gene-dosage modulation are different strategies with different targets and risks.

10-YEAR TAKEAWAY

An ethical decision weighs benefit, harm, autonomy, heritability, access, and alternatives before technical possibility.

Socratic launch

Show the analogy panel only: A community bridge decision needs more than an engineer. Do not name the biology yet.

- Who experiences the benefits and risks?
- Which voices are missing if only engineers decide?
- How does an irreversible choice change the process?

Rules students should earn

- Separate somatic from germline effects.
- Compare intervention with effective existing care.
- Include affected communities and equity in governance.

Biology reveal and evidence

ID	Finding supplied in the case
GEN19-E1	Cleft lip and palate already have effective multidisciplinary treatments, though access is unequal.
GEN19-E2	Germline editing could affect future generations who cannot consent.
GEN19-E3	Access to cleft care and new technology is uneven.

Decision and answer guidance

Situation: A proposed germline intervention may reduce cleft risk but has uncertain off-target effects and high cost.

Strongest option: Pause approval and require stronger safety, governance, community input, and access planning.

Evidence required: GEN19-E1 + GEN19-E2

Claim ceiling: You may reason from the supplied case. You may not claim one universal moral answer for every family or future technology.

Next handoff: We have now followed the gene from the first clue all the way to treatment and the ethics of treatment. Nothing is left to…

TEACHER PLAN 20 OF 20 | WHOLE TEAM (HEAD MEDICAL GENETICIST AND ALL SPECIALIST SEATS)

What Is Mateo's Complete Genetic Story?

Assemble the full genetic workup into a structured Domain Report that connects clue, gene, variant, protein, network, proof, population, risk, treatment, and ethics into one coherent argument.

CARRY FORWARD

An ethical decision weighs benefit, harm, autonomy, heritability, access, and alternatives before technical possibility.

10-YEAR TAKEAWAY

Mateo's strongest genetic story is multifactorial and evidence-bounded: IRF6 explains a pathway, not a proven individual cause.

Socratic launch

Show the analogy panel only: A courtroom file separates facts, expert models, and unresolved claims. Do not name the biology yet.

- Which items are direct case facts?
- Which items come from research models?
- Which claim remains unresolved without a molecular result?

Rules students should earn

- Separate patient evidence from exemplar-gene evidence.
- Link variant to molecule to cell to tissue when supported.
- End at the claim ceiling, not the most dramatic story.

Biology reveal and evidence

ID	Finding supplied in the case
GEN20-E1	Mateo has an isolated-appearing cleft and no strong family pattern in the composite file.
GEN20-E2	IRF6 coding and regulatory studies explain how epithelial differentiation and cleft risk can change.
GEN20-E3	No pathogenic IRF6 result or single causal exposure is supplied for Mateo.

Decision and answer guidance

Situation: The team must approve one conclusion that will be shared with every other domain.

Strongest option: Use a multifactorial, IRF6-informed model while stating that Mateo's cause is unproven.

Evidence required: GEN20-E1 + GEN20-E2

Claim ceiling: You may synthesize the best-supported model. You may not add a molecular diagnosis absent from the case file.

Next handoff: The genetics team has now assembled Mateo's complete molecular story, from first clue to ethics. But genetics cannot finish his care alone. We hand…