MT-RNR1 Advanced Pharmacogenomics Competency
An \textit{MT-RNR1} high-risk genotype is associated with aminoglycoside-induced \underline{________.}

a) High-frequency hearing loss
b) Vestibular toxicity
c) Renal toxicity
d) None of the above
Which of the following MT-RNR1 variants are associated with aminoglycoside-induced hearing loss?

a) m.1494T
b) m.1095C
c) m.1555G
d) All of the above
A patient who has the “Increased Risk of Aminoglycoside-induced Hearing Loss” phenotype is prescribed amikacin. Which of the following actions is most appropriate based on the MT-RNR1 phenotype?

a) Dispense amikacin as prescribed
b) Substitute tobramycin for amikacin
c) Select a non-aminoglycoside antibiotic
d) Prescribe a reduced dose of amikacin
Objectives

Upon completion of this competency, participants will be able to:

– Recognize the high-risk *MT-RNR1* allele variants
– Assign the correct MT-RNR1 phenotype based on a patient’s *MT-RNR1* genotype
– Make therapeutic recommendations for aminoglycoside therapy based on a patient’s *MT-RNR1* pharmacogenetic test result
– Identify sections of the EHR with *MT-RNR1* test-related information
A 3-year-old boy who is receiving therapy for acute lymphoblastic leukemia presents to the hospital with fever and neutropenia. He is initially treated with cefepime.

While flushing the catheter after the cefepime infusion, he develops chills and rigors, so amikacin is prescribed.

An alert is presented to the prescriber indicating that the patient is at high risk of ototoxicity from amikacin due to his MT-RNR1 genotype test result.
What is *MT-RNR1*?
Mitochondrial DNA

• Human cells have two sets of DNA:
  – Chromosomal DNA inherited from both parents
  – Mitochondrial DNA inherited from the mother

• Because chromosomal DNA are inherited from both parents, individuals have **two alleles for each gene**:
  – For example: *CYP2C19* *1/*17

• Because mitochondrial DNA is inherited from one parent (the mother), there is only **one allele per gene**:
  – For example: *MT-RNR1* m.1555G
MT-RNR1 gene

- *MT-RNR1* is a gene in the mitochondrial DNA that codes for the 12S ribosomal RNA (rRNA)
- Certain genetic variations in the *MT-RNR1* gene lead to changes in the shape of the ribosome, which can make the human ribosome look more like bacterial ribosomes

MT-RNR1 Encodes rRNA

Bacterial rRNA

5’ 3’
G—C  
G—C  
C—G  
G—C  
U  U  
C—G  
A  A  
A  A  
1409 1491
C—G
A—U
C—G
C—G

Normal Human rRNA

5’ 3’
G—C  
G—C  
C—G  
G—C  
U  U  
C—G  
A  A  
A  A  
1494 1555
C—C
C—A
C—G
U—A
C—G
C—G
C—G

Human rRNA with MT-RNR1 1555G variant

5’ 3’
G—C  
G—C  
C—G  
G—C  
U  U  
C—G  
A  A  
A  A  
1494 1555
C—C
C—G
C—G
U—A
C—G
C—G
C—G

MT-RNR1 Encodes rRNA

Bacterial rRNA

5' 3'
G—C
G—C
G—C
C—G
G—C
G—C
U  U
C—G
A—U
C—G
C—G

1409 → 1491
C—G
A—A
C—G
A—U
C—G
C—G

Normal Human rRNA

5' 3'
G—C
G—C
G—C
C—G
G—C
U  U
C—G
A—A
C—C
C—A
C—G
U—A
C—G
C—G
C—G

1494 → 1555
C—A
C—G
C—G
U—A
C—G
C—G
C—G

Human rRNA with MT-RNR1 1555G variant

5' 3'
G—C
G—C
C—G
G—C
G—C
U  U
C—G
A—A
C—C
C—G
C—G
U—A
C—G
C—G

1494 → 1555
C—G
C—G
C—G
C—G
C—G

MT-RNR1 and aminoglycosides

- Aminoglycosides work by binding to bacterial ribosomes.
- When variations in the MT-RNR1 gene cause the human ribosome to look more like bacterial ribosomes, aminoglycosides lose their specificity for bacterial ribosomes and also bind to human ribosomes.
- The goal is to know the patient’s MT-RNR1 status prior to a patient receiving the first dose of an aminoglycoside.
MT-RNR1 Allele Variants
• There are three known high-risk *MT-RNR1* variants:
  
  – *m.1555G*
  
  – *m.1494T*
  
  – *m.1095C*
Assigning MT-RNR1 phenotypes
MT-RNR1 Phenotypes

- The assignment of MT-RNR1 phenotype is based on the mitochondrial \textit{MT-RNR1} allele that the patient carries
- Reminder: there is no diplotype because only one allele is inherited for a mitochondrial gene
- There are \textbf{two} MT-RNR1 phenotypes
  - Increased Risk of Aminoglycoside-induced Hearing Loss
  - Normal Risk of Aminoglycoside-induced Hearing Loss
MT-RNR1 Phenotypes

- Increased Risk of Aminoglycoside-induced Hearing Loss
  - Assigned to individuals carrying one high-risk \textit{MT-RNR1} allele
  - This is the high-risk phenotype
  - Approximately \textit{0.1\% (1 in 1,000)} individuals have this phenotype
  - It is defined by the presence of any of the high-risk \textit{MT-RNR1} alleles
    - \textit{m.1555G}
    - \textit{m.1494T}
    - \textit{m.1095C}
Normal risk of developing hearing loss due to aminoglycoside antibiotics: 99.8%

Increased risk of developing hearing loss due to aminoglycoside antibiotics: 0.2%
MT-RNR1 Phenotype-based Recommendations for Aminoglycosides
Aminoglycosides are antibiotics used to treat Gram-negative and some Gram-positive infections. They include agents such as:
- Amikacin, gentamicin, plazomicin, streptomycin, and tobramycin.

Formulations and routes of delivery
- MT-RNR1 phenotype should be considered for aminoglycosides given by the intravenous and inhaled routes as these are absorbed systemically.
- MT-RNR1 phenotype is less of a consideration if aminoglycosides that are given by the ophthalmic or topical routes given their low systemic absorption.
  - Reminder: otic formulations should be avoided in all patients (regardless of MT-RNR1 phenotype) if the tympanic membrane is ruptured, including in someone with tympanostomy tubes.
Patients with the Increased Risk of Aminoglycoside-induced Hearing Loss phenotype are at high risk of developing hearing loss after exposure to aminoglycosides:

- Risk of hearing loss applies to all aminoglycosides
- Hearing loss typically starts as a high-frequency hearing loss, which can progress to profound deafness
- Hearing loss is bilateral and irreversible
- In people with this phenotype, hearing loss occurrence is independent of the duration and dose and can occur even after a single dose of aminoglycoside
• Depending on your institution, the Infectious Diseases Service or the Antimicrobial Stewardship team should be consulted ASAP if you are considering to prescribe an aminoglycoside agent to a patient with the MT-RNR1 high-risk phenotype.

• Avoid prescribing aminoglycosides antibiotics
  – Unless the high risk of permanent hearing loss outweighs the severity of infection and there is a lack of safe effective alternative therapies.

• Prescribe an alternative agent
  – Consider patient specific factors and clinical status, such as culture results and colonization history when selecting the alternative agent.
Note: It is important to consider patient-specific factors, and the CDS alert will not provide a “blanket” alternative recommendation.
Patients with the Normal Risk of Aminoglycoside-induced Hearing Loss are at normal risk of developing hearing loss after exposure to aminoglycosides

- No change in therapy is warranted based on the MT-RNR1 test result alone
- **Note:** Patients with this phenotype are still at risk of developing hearing loss from aminoglycosides, but the risk is the same as most people
For More Information…

• For more information about MT-RNR1 and aminoglycoside therapy, visit the CPIC guideline at https://cpicpgx.org/gene/MT-RNR1

• For more information about the St. Jude implementation efforts for MT-RNR1 visit www.stjude.org/mtrnr1
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Correct Answer: A
Which of the following \textit{MT-RNR1} variants are associated with aminoglycoside-induced hearing loss?

\begin{itemize}
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  \item [b)] \textit{m.1095C}
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Correct Answer: D
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Correct Answer: C
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