MT-RNR1 Advanced Pharmacogenomics Competency

Updated on 5/2022

Pre-Test Question #1

An *MT-RNR1* high-risk genotype is associated with aminoglycoside-induced _____.

a) High-frequency hearing loss

b) Vestibular toxicity

c) Renal toxicity

d) None of the above

Pre-Test Question #2

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

Pre-Test Question #3

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

Patient Case

- 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

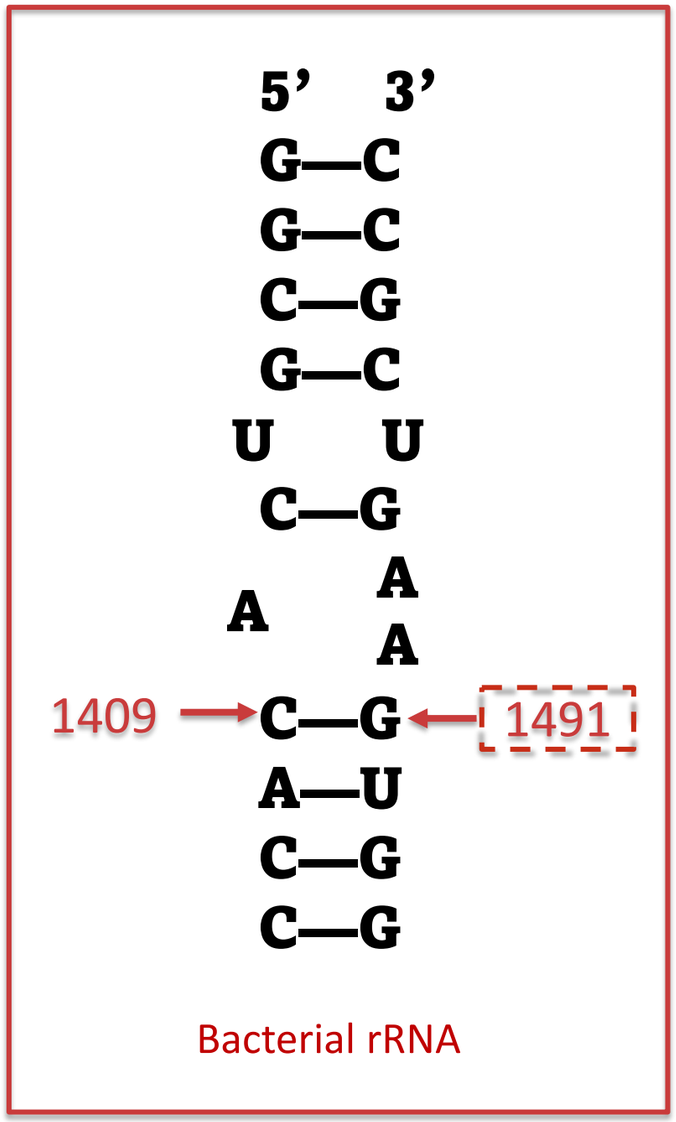
- Human cells have two sets of DNA:
  - Chromosomal DNA inherited from both parents
  - Mitochondrial DNA inherited from the mother
- Because chromosomal DNA are inherited from both parents, individuals have **two alleles for each gene**:
  - For example: *CYP2C19 *1/*17*
- Because mitochondrial DNA is inherited from one parent (the mother), there is only one allele per gene:
  - For example: *MT-RNR1 m.1555G*

MT-RNR1 gene

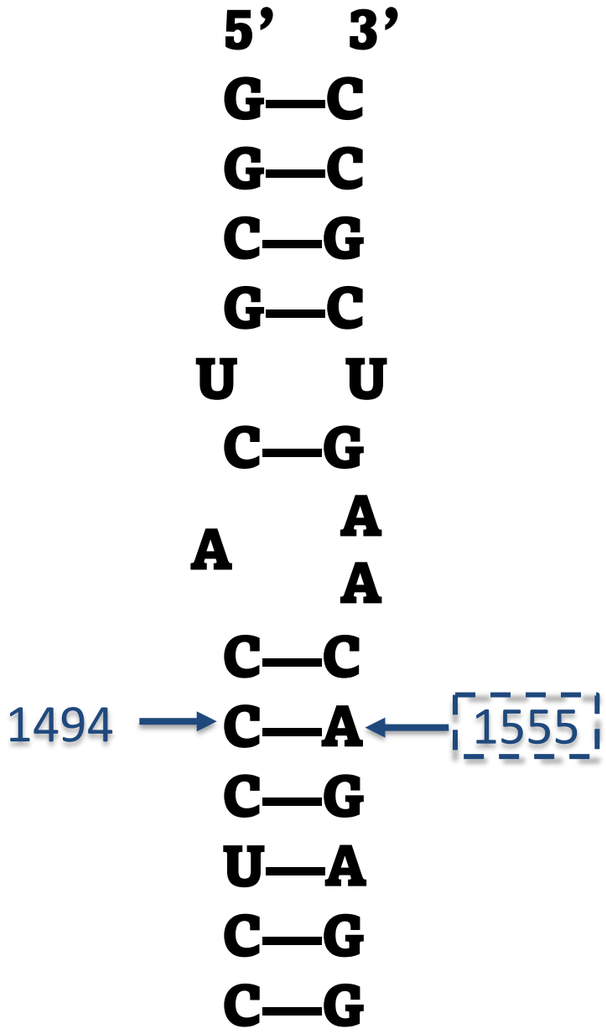
- *MT-RNR1* is a gene in the mitochondrial DNA that codes for the **12S ribosomal RNA (rRNA)**
- Certain genetic variations in the *MT-RNR1* gene lead to changes in the shape of the ribosome, which can make the human ribosome look more like bacterial ribosomes

Barbarino JM et al. *Pharmacogenet Genomics*. 2016;26:558.

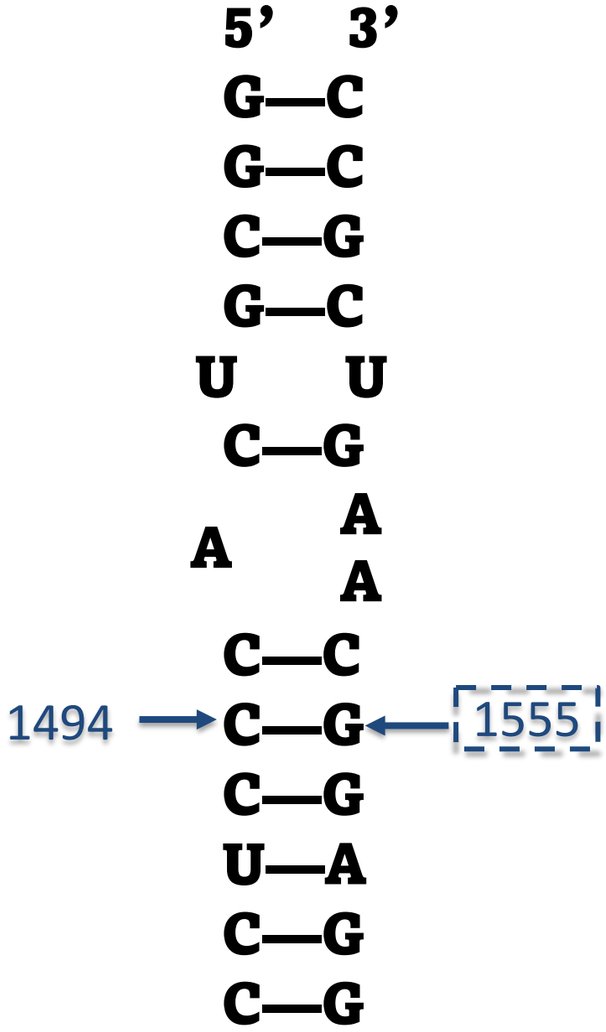
MT-RNR1 Encodes rRNA



Bacterial rRNA

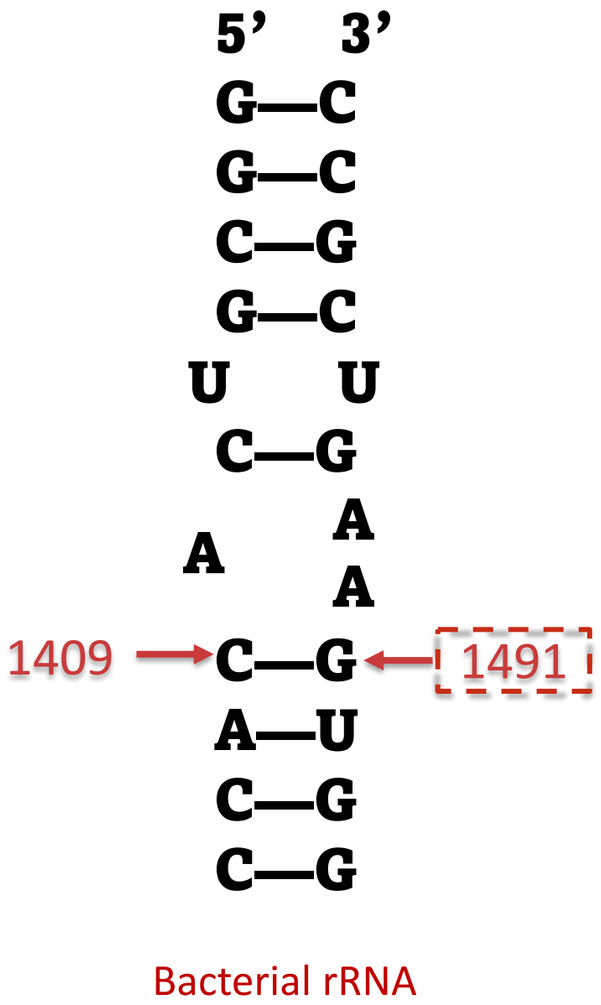


Normal Human rRNA

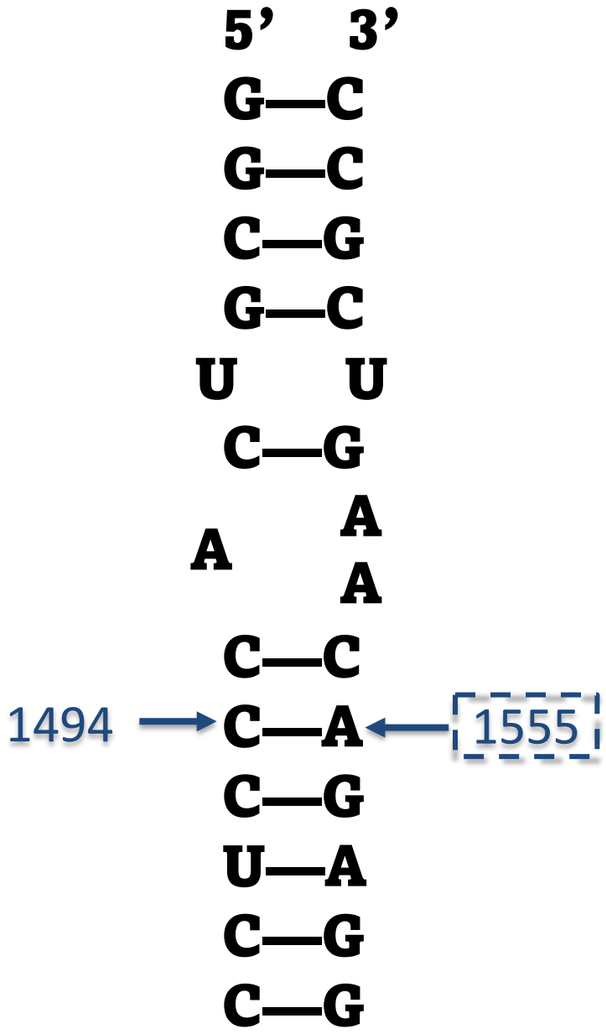


Human rRNA with *MT-RNR1 1555G* variant

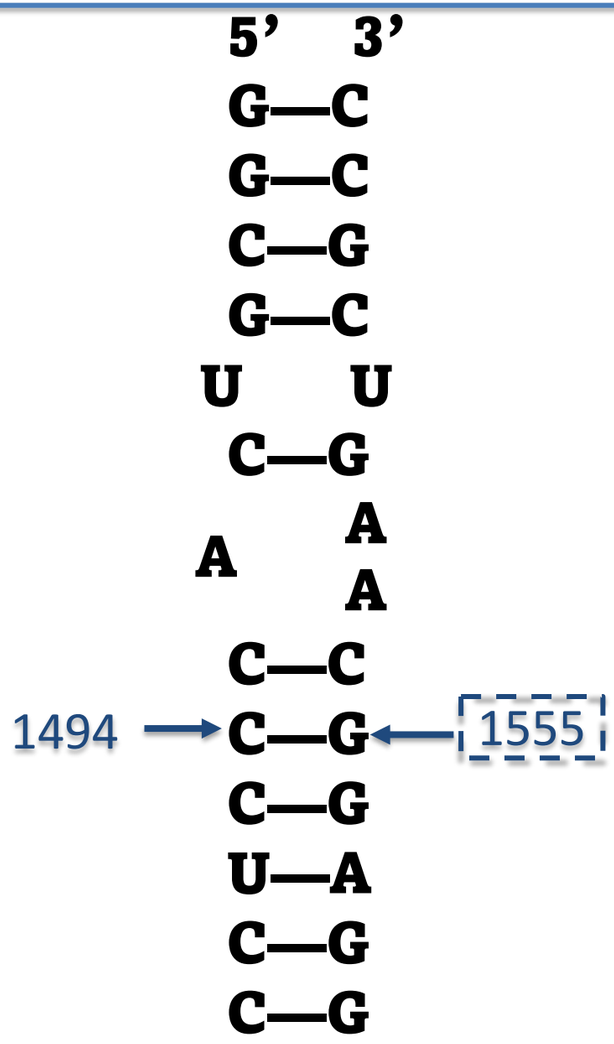
MT-RNR1 Encodes rRNA



Bacterial rRNA



Normal Human rRNA



Human rRNA with *MT-RNR1 1555G* variant

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

MT-RNR1 High-Risk Alleles

- There are three known high-risk *MT-RNR1* variants:
  - *m.1555G*
  - *m.1494T*
  - *m.1095C*

Assigning MT-RNR1 phenotypes

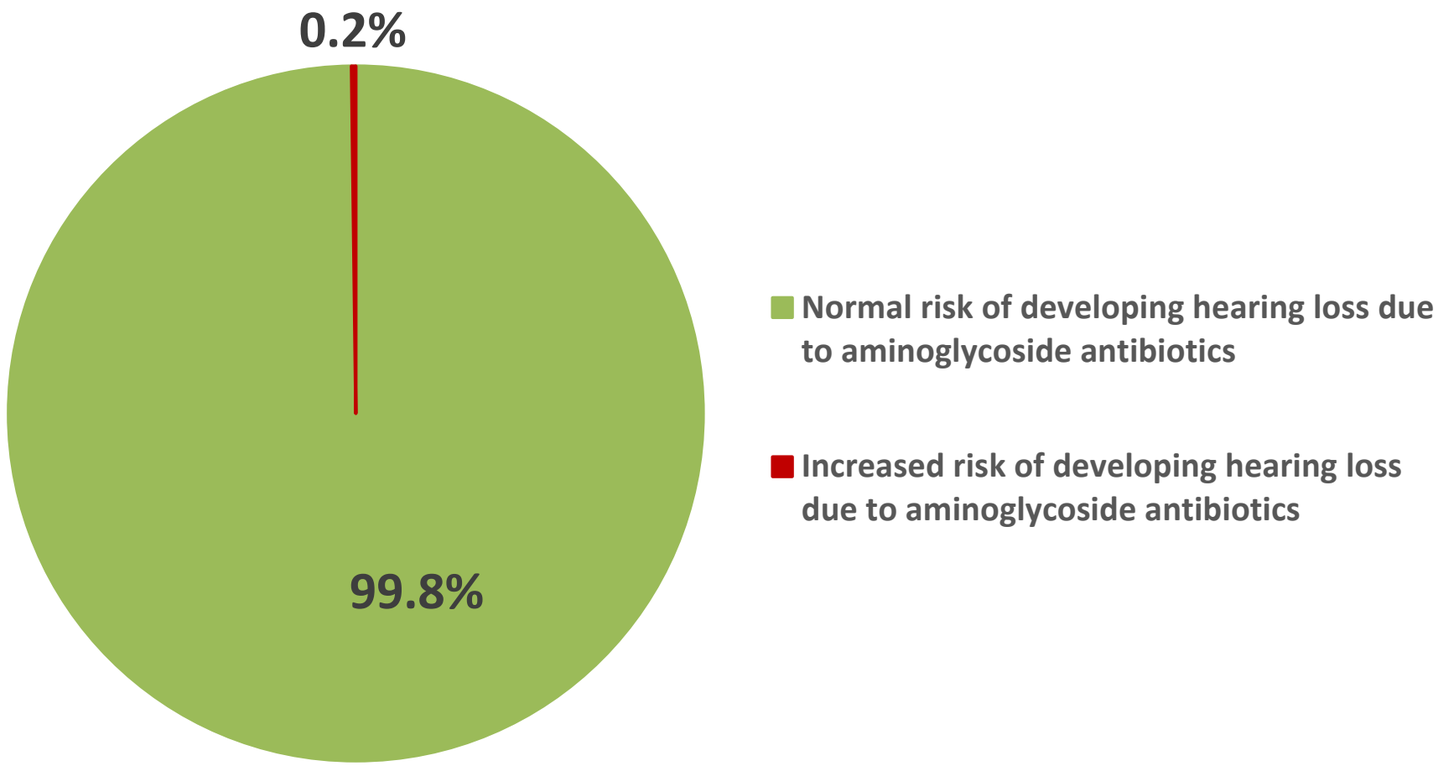
MT-RNR1 Phenotypes

- The assignment of MT-RNR1 phenotype is based on the mitochondrial *MT-RNR1* allele that the patient carries
  - Reminder: there is no diplotype because only one allele is inherited for a mitochondrial gene
- There are 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 *MT-RNR1* allele
    - This is the high-risk phenotype
    - Approximately **0.1% (1 in 1,000)** individuals have this phenotype
    - It is defined by the presence of any of the high-risk *MT-RNR1* alleles
      - *m.1555G*
      - *m.1494T*
      - *m.1095C*

MT-RNR1 Phenotype Prevalence



McDermott JH, et al. *Clin Pharmacol Ther*. 2022;111:366.

MT-RNR1 Phenotype-based Recommendations for Aminoglycosides

Aminoglycosides and MT-RNR1 Phenotypes

- 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.

Rosenfeld RM, et al. *Otolaryngol Head Neck Surg*. 2014;150(1 Suppl):S1-S24.
McDermott JH, et al. *Clin Pharmacol Ther*. 2022;111:366.

MT-RNR1 High-risk Phenotype and Aminoglycosides

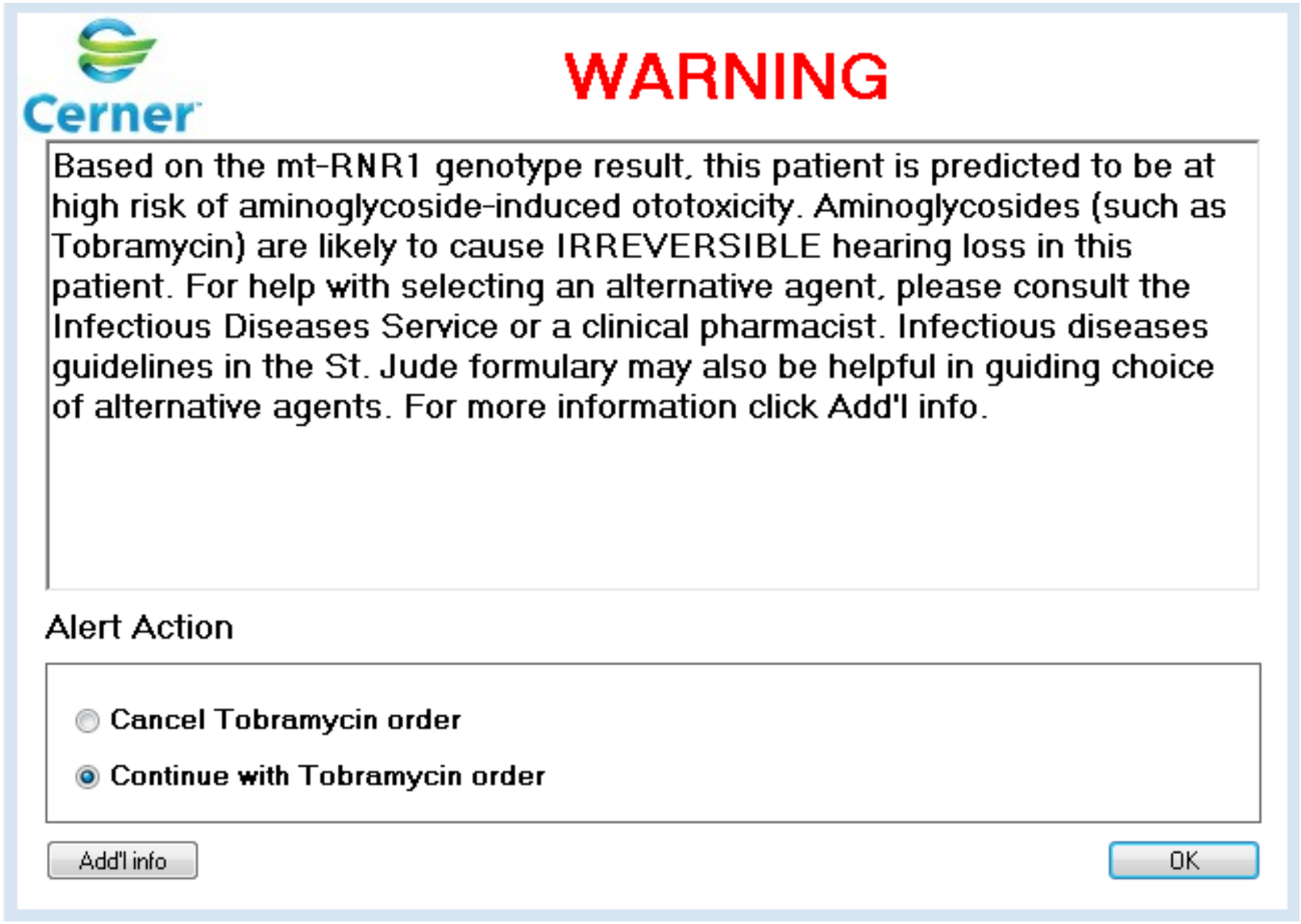
- Patients with the Increased Risk of Aminoglycoside-induced Hearing Loss phenotype are at high risk of developing hearing loss after exposure to aminoglycosides:
  - Risk of hearing loss applies to all aminoglycosides
  - Hearing loss typically starts as a high-frequency hearing loss, which can progress 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

McDermott JH, et al. *Clin Pharmacol Ther*. 2022;111:366.
Guan MX, et al. *Mitochondrion*. 2011;11:237.

MT-RNR1 High-risk Phenotype & Aminoglycosides Considerations

- 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

Example Clinical Decision Support Alert



Note: It is important to consider patient-specific factors, and the CDS alert will <u>not</u> provide a “blanket” alternative recommendation.

Normal Risk of Aminoglycoside-induced Hearing Loss

- 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

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Correct Answer: D

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Correct Answer: C

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