**INSTRUCTORS’ GUIDE TO “THE FOREVER FIX: GENE THERAPY AND THE BOY WHO SAVED IT”**

1. Imagine your young child is diagnosed with a rare inherited disease. List ways to learn about the disease, find clinical trials, and raise funds.

2. What is gene therapy?

3. How does the structure of a virus enable it to be used to deliver gene therapy?

4. What are the technical challenges in developing a gene therapy that is effective?

5. Explain how Corey Haas, Hannah Sames, and Max Randell each has inherited a disease, but have no other affected family members.

6. What was the significance of the fact that Corey’s electroretinogram (ERG) was “as flat as an Iowa cornfield”?

7. How is Corey’s gene therapy different from enzyme replacement therapy?

8. Explain the difference in the mode of inheritance of Corey’s disease (LCA2) and Jesse Gelsinger’s disease (OTC deficiency).

9. Why didn’t Corey’s local pediatrician suspect a genetic disease?

10. Explain how Corey could have been losing vision even though his rods and cones were still healthy.

11. Describe the exact effect of Corey’s mutations on his retinas.

12. Explain how gene therapies would differ for different forms of Leber congenital amaurosis.

13. Describe a phenocopy of LCA (an environmental cause of the same symptoms).

14. Describe two other genetic diseases that Corey’s symptoms resembled.

15. Select a different genetic disease and list other conditions that might be part of the “differential diagnosis” that a physician uses to narrow down possibilities.

16. Corey is a “compound heterozygote.” What does this mean?

17. Why couldn’t eating a lot of carrots treat Corey’s disease?

18. Explain why gene therapy for Corey will likely be a permanent solution to his problem, but will not be passed on to his children.

19. The cells that received the gene therapy in Corey’s eyes do not divide. The genes delivered to his eyes remained outside his chromosomes, as DNA rings. What would happen if the targeted cells divide and the healing genes do not integrate into chromosomes?

20. Why was Jesse Gelsinger’s experience with OTC deficiency much milder than that of most babies with the disease?

21. Do you think that Jesse Gelsinger gave truly informed consent for gene therapy? What information that he and his father did not know might have influenced their decision to agree to participate in the experiment?

22. How does a phase 1 clinical trial differ from a phase 1/2 trial?

23. What is the major challenge of carrying out a phase 3 clinical trial?

24. Explain how ADA deficiency and SCID-X1 differ, and how they are alike.

25. Why did Ashi DeSilva’s doctors continue to give her enzyme replacement therapy while she had gene therapy? How did the enzyme treatment complicate interpretation of the gene therapy experiment?

26. How did gene therapy for SCID-X1 cause leukemia?

27. How can researchers safely use HIV to carry healing genes in gene therapy? Why is HIV a good vector?

28. Why can adrenoleukodystrophy (ALD) be treated with gene therapy introduced into the bloodstream, whereas gene therapy for Canavan disease must be given through holes bored into a child’s skull?

29. Explain the differences in the biochemical causes of ALD and Canavan disease. How are the two diseases similar?

30. How can different demyelinating diseases have different causes?

31. How is giant axonal neuropathy different from a muscular dystrophy?

32. Name the parts of the cell that are affected in ALD and GAN.

33. Explain how animals helped researchers to develop gene therapy for two of the diseases discussed in the book.

34. At what age do you think a child is competent to give informed consent? How would you explain gene therapy to an 8-year-old?

35. Choose a disease and propose a gene therapy for it. Include which cells and which parts of them would be targeted, which vector or other method would introduce the gene, and how the experiment would be conducted as safely as possible.

36. Discuss the difficulties of conducting a gene therapy trial for a very rare disease.

37. Choose a common disease and explain how gene therapy might be used to treat or cure it.

38. Choose one of the researchers or physicians in the book and discuss the high points and challenges of their careers.