# Pharmacogenetics: Using Genetics to Treat Disease*

*by*
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It's called the children's ward. For two teenagers who have been recently diagnosed with leukemia, it seems insulting to have their lives hijacked by doctors and nurses with stuffed animals clipped to their stethoscopes. Laura is a forward on her school soccer team and leads the league in scoring. For the last four months, she has been really tired, but nothing seemed really wrong until her legs became covered with bruises. Just pressing her fingers on her skin was practically enough to make a bruise. It didn't seem real when her doctor, Jane Ryder, diagnosed her with Acute Lymphocytic (or Lymphoblastic) Leukemia (ALL), or when she told her that ALL is the most common malignant (spreading) cancer found in children. She's 14 years old; she's not a child!

Beth is 13 and looks remarkably like Laura. Both have straight dark hair, large brown eyes, and tall slender builds. Beth has never been that athletic; she prefers reading and theater. She's hoping to be part of the drama
team next year when she goes to high school, even though she'll only be a freshman. But she's been missing a lot of school because of one virus after another, lots of fevers and night sweats, then that rash in the fall. Now she's in a hospital, and it seems like the only people she sees are her parents, Dr. Ryder, and the nurses.

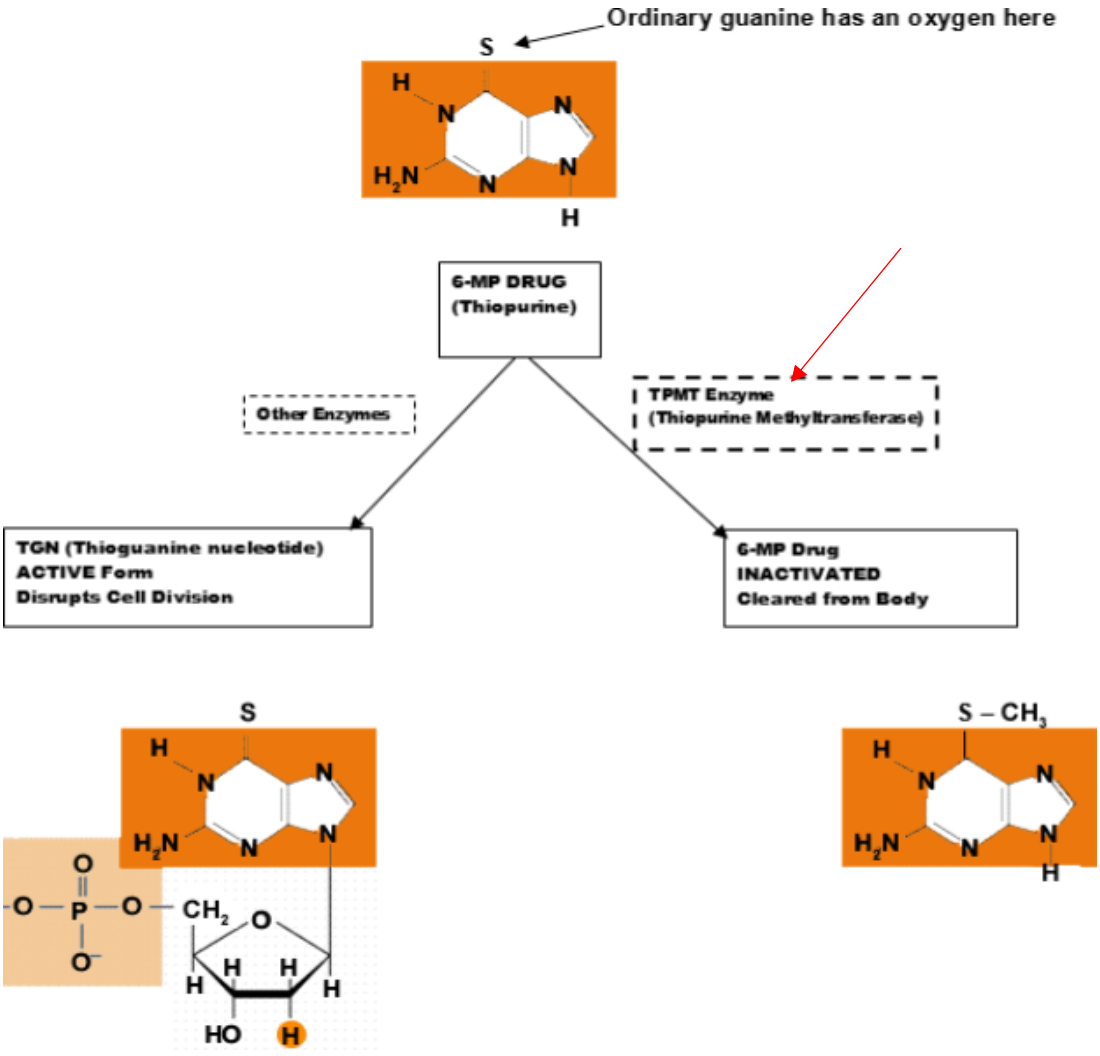
Laura and Beth both have ALL, which arises from the uncontrolled growth of immature lymphocytes (a type of white blood cell, or leukocyte). These cells, which are "stuck" in an early stage of development, become so numerous that they crowd out normal blood cells. Each year about 30 cases occur per million people, and most of those cases are in children aged 2–5 years. The cause of ALL remains largely unknown, although a small number of cases are associated with inherited genetic syndromes. Both girls are suffering from anemia (low blood cell levels), fevers, bleeding, and are pale and thin. Dr. Ryder has decided to treat them as in-patients, keeping them in the hospital while treating them with a "thiopurine" drug called 6-mercaptopurine (6-MP) known to be highly effective in treating leukemia. The medication interferes with DNA replication and stop rapidly growing cells like cancer cells from further growth. Unfortunately, they also block the growth of other fast growing cells needed for good health, like the cells in the bone marrow that develop into erythrocytes (red blood cells) and leukocytes.

As with many drugs given as chemotherapy, it is important to give a high enough dosage to prevent cancer cells from replicating, while avoiding damage to the normal tissues. Too high a drug dose can be very toxic. Dr. Ryder knows that drugs are processed in various ways in the body. They must be absorbed by the blood, distributed throughout the body's tissues, converted or transformed into forms that are easier to eliminate, and then removed from the body. Dr. Ryder gives both girls the same dosage of the drug before leaving the hospital for the night.

While making her rounds over the next few days, Dr. Ryder sees Laura's vital signs plummet. Her anemia has worsened; her erythrocyte count is so low that her heart function could be compromised. Her fevers are spiking, and her breathing is becoming shallow and labored. She is not eating and is being hydrated intravenously. Her condition is life-threatening. In contrast, Beth's anemia has decreased, she is free of fever,

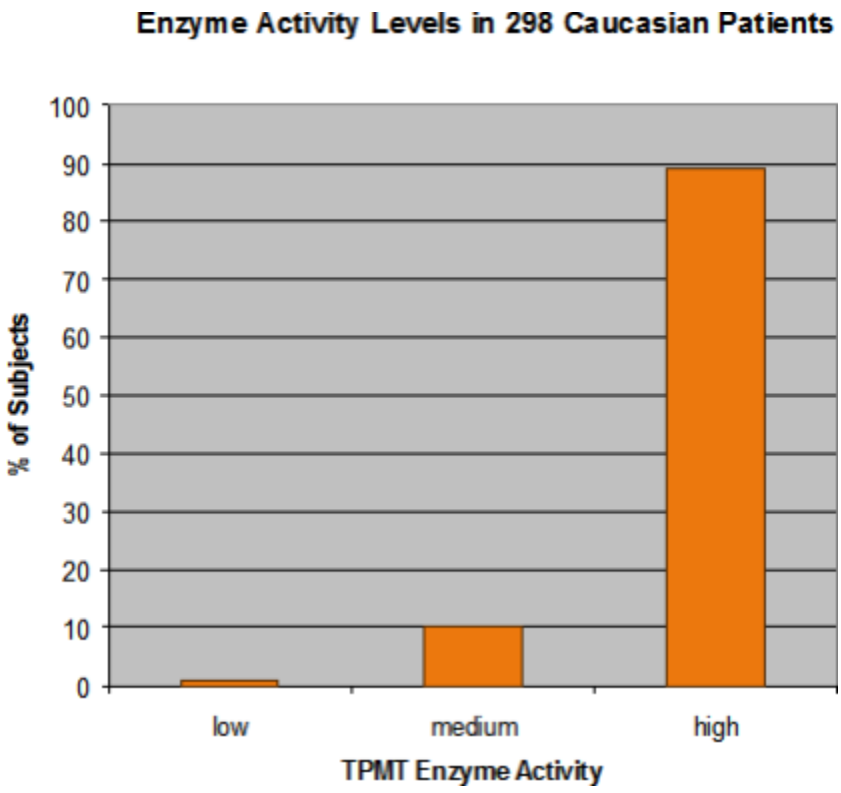
and is actually showing signs of an appetite and boredom, good indicators of improved health. Dr. Ryder had not anticipated that the drug could act so differently in two individuals. Even as she looks at Beth's chart, she can picture Laura's body struggling to hold its own just two private rooms away. Dr. Ryder knows she must find out why her patients are responding so differently. But where should she start, and will she find an answer in time to help Laura?

Dr. Ryder learns that the difference in patient reaction to the drug probably has something to do with how the drug is naturally metabolized in the body to be removed as waste. After searching the scientific literature, she learns that the drug 6-MP can either be converted to the active form, TGN nucleotides, or can be inactivated with the help of the TPMT enzyme. Within each patient who takes the drug, both processes are occurring and they compete with each other.




Since the therapy aims to harm rapidly replicating cells without overly impacting normal ones, it is important that excess drug is inactivated. Dr. Ryder decides to see how levels of the TPMT enzyme activity might vary between people.

She reviews the research papers that have been published about the TPMT enzyme and finds an interesting graph. From a study of 298 randomly selected Caucasian individuals, researchers found the following levels of TPMT enzyme activity:




## Questions

1. **If Dr. Ryder had 10 Caucasian patients in the next month, how many would you predict to have each of the TPMT enzyme activity levels, based on the graph above?**

**Low:**

**Medium:**

**High:**

**2. Each individual inherits two copies of the gene for the enzyme, one from each parent. Dr. Ryder suspects that variation in enzyme activity level is controlled by two different versions (alleles) of that gene. Does this graph (and the number of phenotypes) suggest that enzyme activity levels are based on a dominant/recessive or a codominant pattern of inheritance? Explain your answer.**

**3. Which bar (low, medium, or high) represents individuals who might be homozygous for a "low enzyme activity'" version of the gene?**

**4. Which bar represents individuals who might be homozygous for a "high enzyme activity" version of the gene?**

**5. Which bar represents heterozygotes?**

Dr. Ryder tested Laura, who was very sick, and found that her TPMT enzyme activity level was extremely low.

**6. Why would individuals with the lowest level of enzyme get the sickest when they take the drug?**

**7. In the paragraphs below, circle the correct answer (high or low, heterozygous or homozygous).**

From her research, Dr. Ryder hypothesized that patients such as Laura (who became very sick upon receiving the drug) have very **high / low** TPMT enzyme activity and therefore very **high / low** levels of TGN nucleotides at normal doses. They easily became sick from the effects of the drug, and could even die. These patients are **homozygous / heterozygous** for the version of the gene encoding **high / low** enzyme activity. A better drug dose for these patients is 1/10th the level of other patients.
Patients such as Beth with **high / low** TPMT enzyme activity had **high / low** levels of TGN nucleotides. These patients would do well with the drug, and in some cases might even need a larger-than-normal dosage for the treatment to be most effective. These patients were either homozygous for the version of the gene encoding **high / low** enzyme activity, or were heterozygous.

Dr. Ryder responded quickly to Laura's drug reaction. She discontinued the drug while alternate treatment regimens were explored, and Laura's condition began to improve.