GENETIC INHERITANCE

Tracing the Past to Prevent Disease in the Future

Mutations in hundreds of genes are associated with high risk for disease. Genes such as *APC, ATM, BRCA1, BRCA2, MLH1, PALB2, TP53*, and many others play a role in cancer. Genes such as *LDLR, LMNA, MYH7*, and many others play a role in heart conditions. For every gene, hundreds to thousands of possible mutations can cause malfunctions, increasing disease risk.

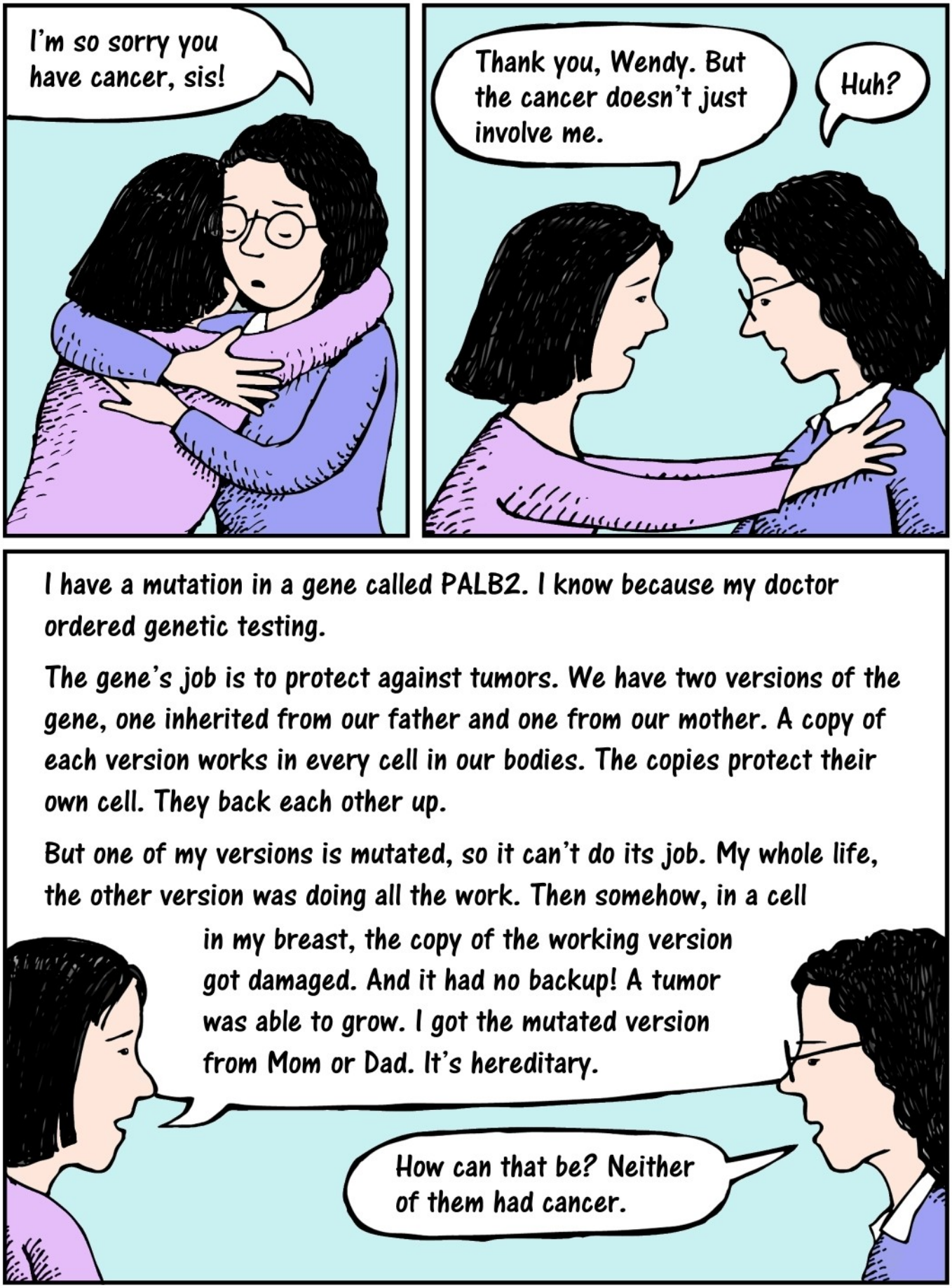
When people know they have a mutation, they can often reduce their risk. They can work with doctors or make lifestyle changes to prevent disease or catch it early. But many people don't have that chance. They don't find out they have a mutation until they already have the disease.

People can find out about genetic risk before disease develops if family members who already know tell them about it. Once a person learns that a disease runs in their family, they can get genetic testing and choose preventative steps that are right for them.

This story illustrates how connecting with genetic relatives when there's a known mutation in the family can help reduce disease risk. And save lives.

CHAPTER ONE

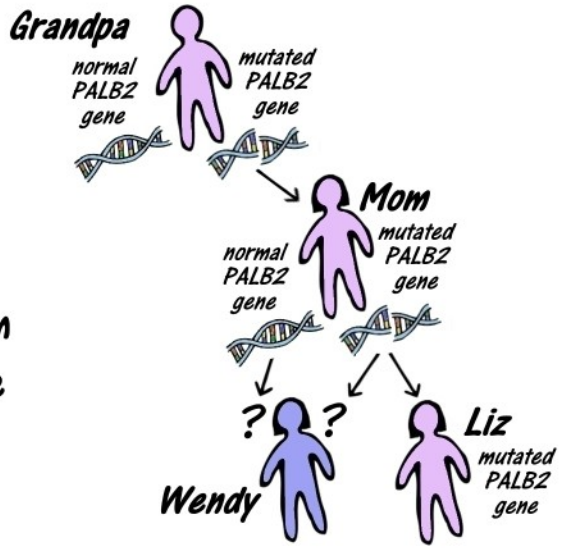
Connecting the Dots


I'm so sorry you have cancer, sis!
Thank you, Wendy. But the cancer doesn't just involve me.
Huh?
I have a mutation in a gene called PALB2. I know because my doctor ordered genetic testing.
The gene's job is to protect against tumors. We have two versions of the gene, one inherited from our father and one from our mother. A copy of each version works in every cell in our bodies. The copies protect their own cell. They back each other up.
But one of my versions is mutated, so it can't do its job. My whole life, the other version was doing all the work. Then somehow, in a cell in my breast, the copy of the working version got damaged. And it had no backup! A tumor was able to grow. I got the mutated version from Mom or Dad. It's hereditary.
How can that be? Neither of them had cancer.

I didn't inherit the disease. I inherited a broken backup system, which made it more likely I'd get the disease. Whichever parent I got it from, their working copies were never badly damaged.

Mom's dad had pancreatic cancer. Maybe he had the mutation?

That would make sense! People only pass one version to each of their children—and it's a random, 50-50 chance which one each child gets. If one of Grandpa's versions was mutated, Mom had a 50-50 chance to get it. And if she inherited the broken version ...

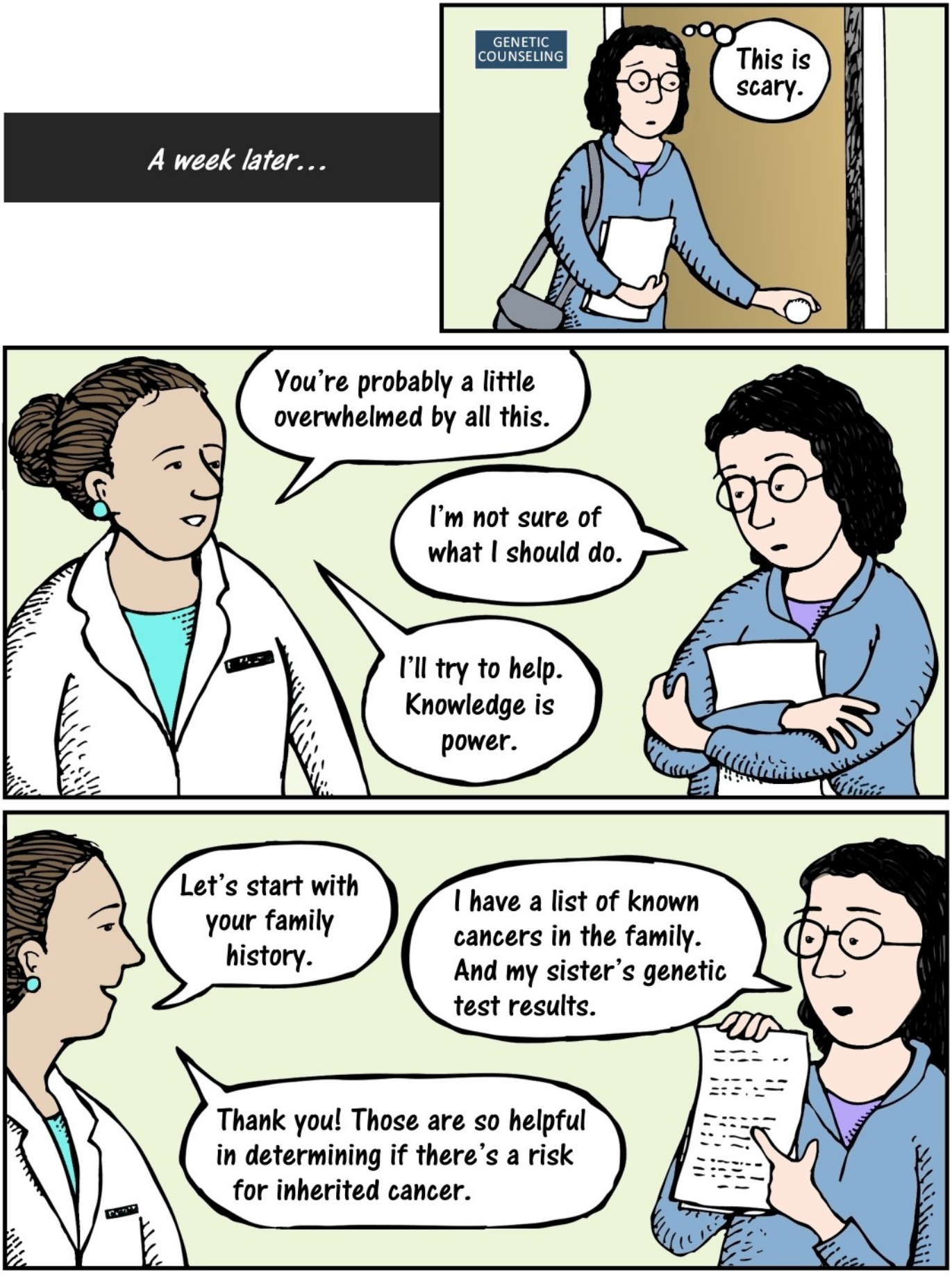


And I did.

...Then you had a 50% chance of getting it from her.

That means there's a 50% chance I have it, too.

Sure does. Millions of people have a mutated version that raises cancer risk. Most don't know they have it. I think you should get tested ASAP.

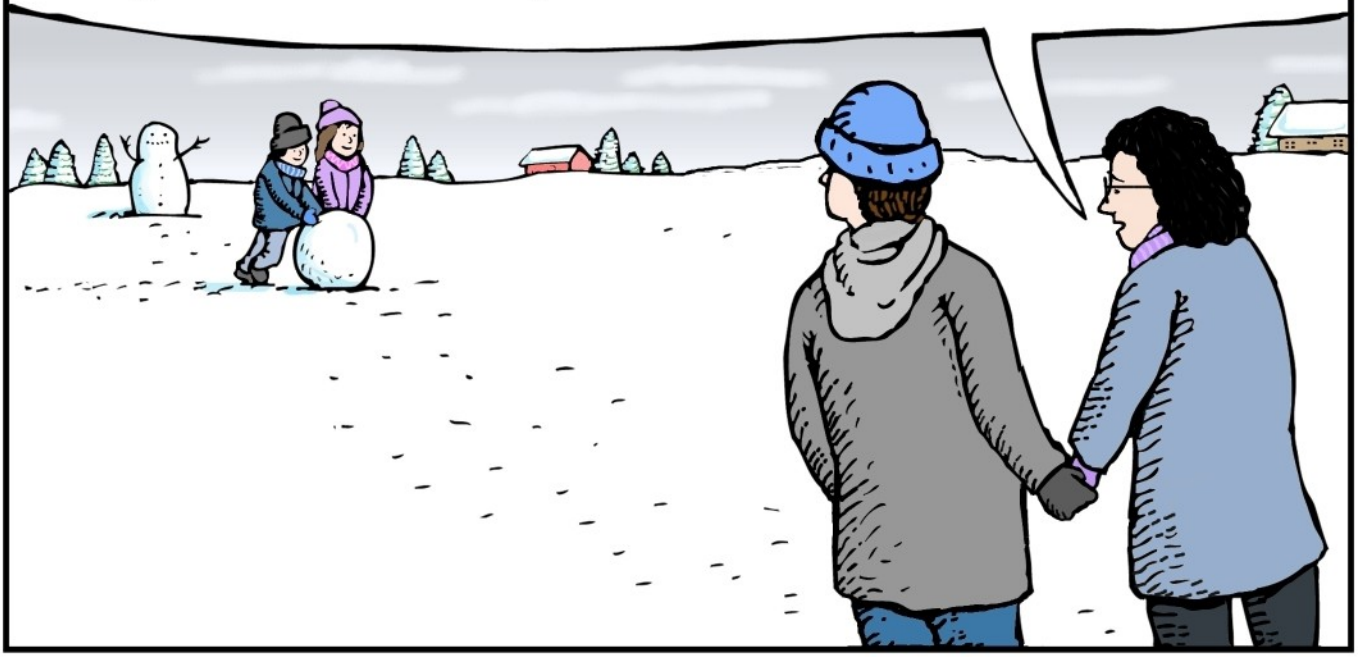

A week later...
GENETIC COUNSELING
This is scary.
You're probably a little overwhelmed by all this.
I'm not sure of what I should do.
I'll try to help. Knowledge is power.
Let's start with your family history.
I have a list of known cancers in the family. And my sister's genetic test results.
Thank you! Those are so helpful in determining if there's a risk for inherited cancer.


Looking over your family history, I would suggest genetic testing.
It's a simple swab of the cheeks. And results should be to you in a couple of weeks. Then we can discuss results after that back here.
Sounds like a good plan to me.
A couple weeks later...
PATIENT:
WENDY D.
#6709-2A
PATHOGENIC
MUTATION IN
PALB2 GENE
c.509_510 del GA
Your genetic counselor will be contacting you soon to discuss results.
Liz, I got my genetic test back. Not the result I was hoping for! What do all the numbers after the gene mean?
Those numbers and letters are code for exactly where the gene mutated, and how. It's what makes our family's version different. That's our unique variant of the gene.

I can't believe I tested positive for that mutation! Will I get cancer? What will happen to them if I do get cancer? And what if they have the mutation, too? Will they get cancer?

And I wonder if there are others out there with this mutation besides us.

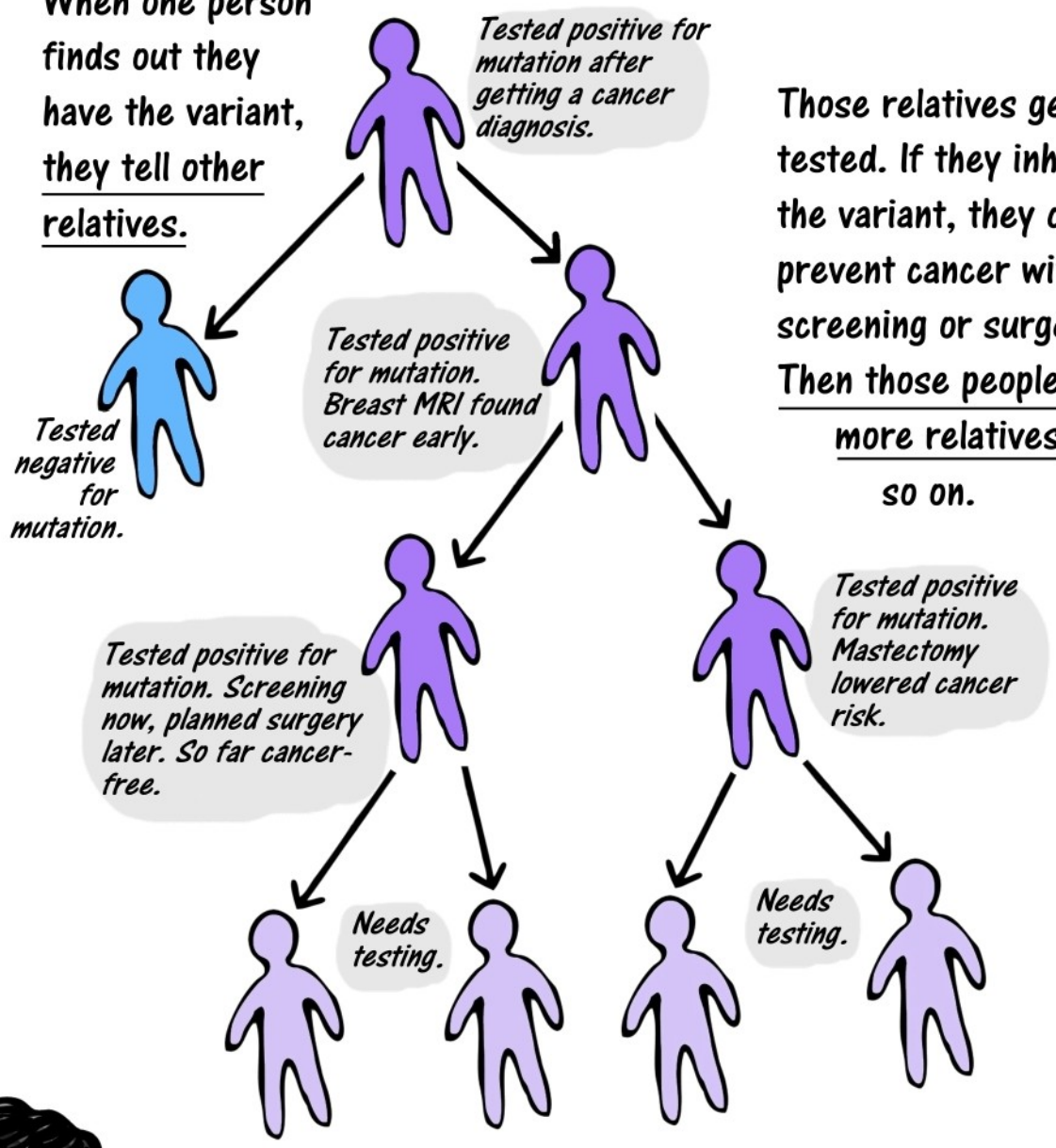
I want to help my family, but I don't know how! I hope when I meet with the genetic counselor I can get some answers.



Now that you know you have a pathogenic variant of PALB2, you can take steps to prevent cancer.

You can protect your family, too. It's called **cascade testing**.

When one person finds out they have the variant, they tell other relatives.



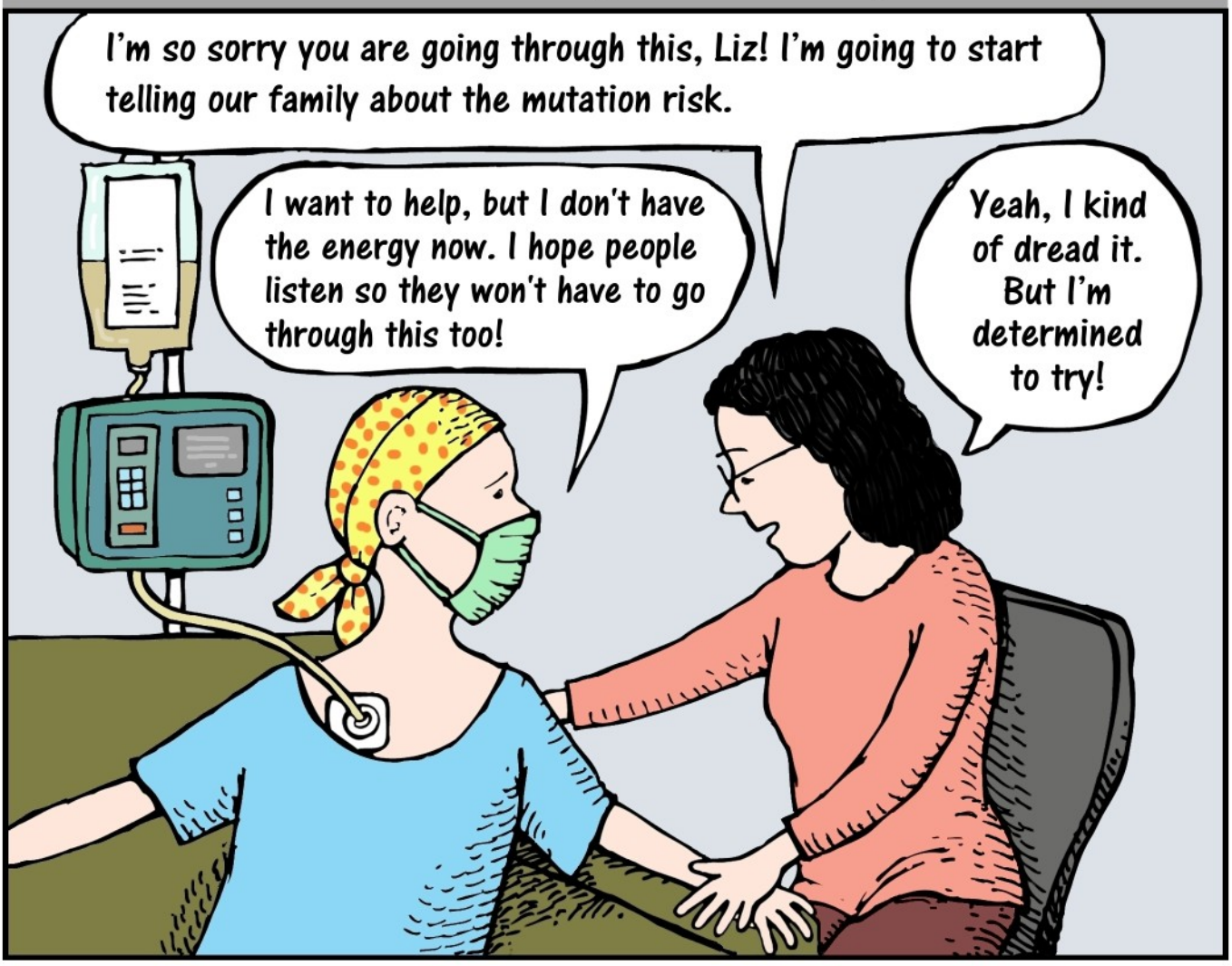
Those relatives get tested. If they inherited the variant, they can prevent cancer with screening or surgeries. Then those people tell more relatives, and so on.

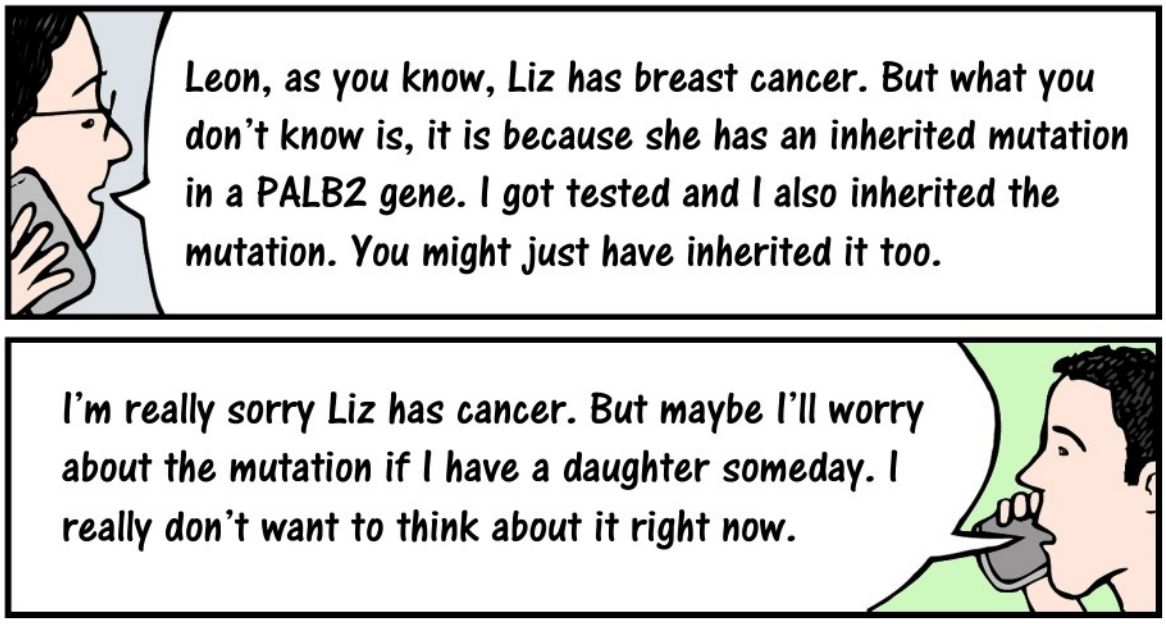
Liz told you. You can tell your brother and your cousins. And you can tell your children when they are old enough.

I don't like calling people with bad news, but I'll do it if it helps my family.

CHAPTER TWO

Connecting the Family






Ugh. I'm not sure I explained the risk very well. Maybe from now on I should just send emails? Would it be better to spell out the risk in black and white?
Sigh. I don't know.
I hate sending emails like this! This is weird—I barely know my aunt. But she should know about the mutation.
She hasn't replied. Should I call her? Was she offended by the email? Maybe I phrased it all wrong. Now what?!
A week later...


What's up, dear?
I'm frustrated! I tried reaching out, but nobody wants to listen! I don't know what to do now!
Maybe there's a group or an organization online that can help? Worth a try.
Nope.
Nothing.
Nil.
Nada.
Ugh.
Wait! Here's something!
"Connect with Relatives. Reduce Inherited Disease Risk."
Sign me up!
ConnectMy
VARIANT
PREVENTION THROUGH CONNECTION
Connect with Relatives. Reduce Inherited Disease Risk.
SIGN UP

A few days later...

Alright! ConnectMyVariant found someone with the same PALB2 variant as me! And she wants to chat with me online.

Hi, I'm Wendy.

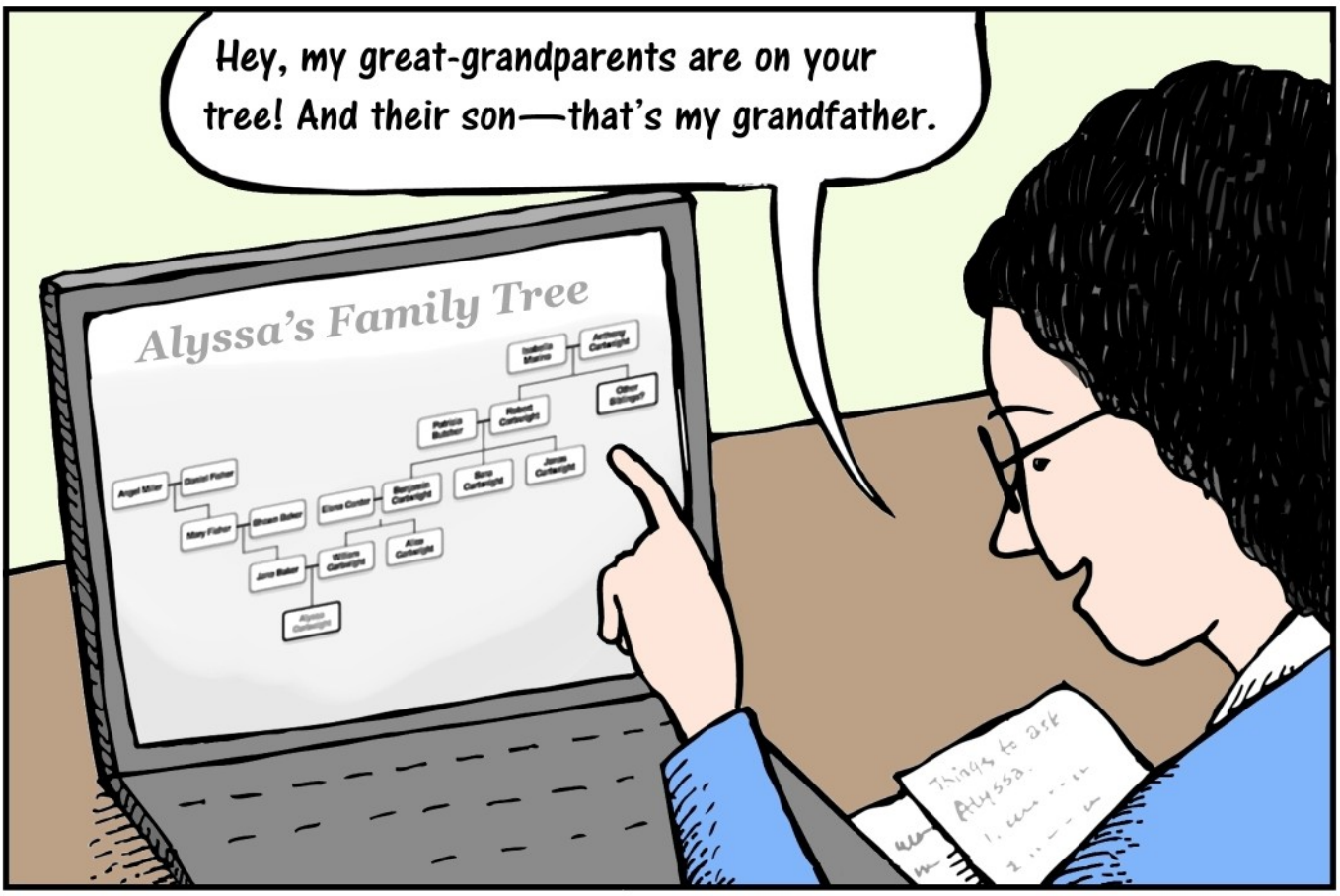
Hi, I'm Alyssa. Great to meet you!

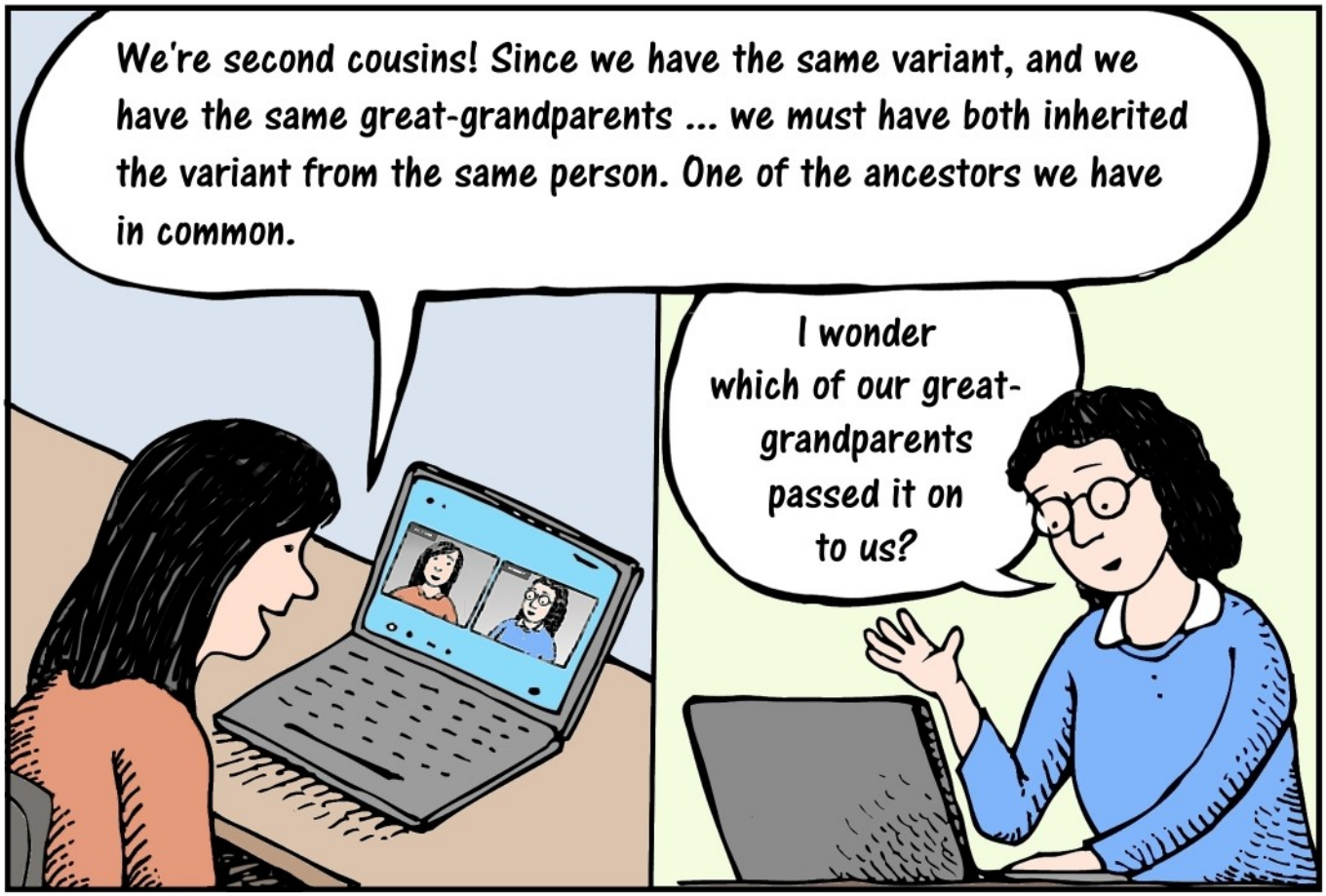
You know, your last name is the same as my mom's maiden name.

There's a good possibility we are related!

Somebody in the past was the first person with this specific variant. They started the chain of passing it to their children. We're likely both descendants of that person.

Let me share my family tree and we'll see.


Hey, my great-grandparents are on your tree! And their son—that's my grandfather.
Alyssa's Family Tree
Things to ask Alyssa.


We're second cousins! Since we have the same variant, and we have the same great-grandparents ... we must have both inherited the variant from the same person. One of the ancestors we have in common.
I wonder which of our great-grandparents passed it on to us?

I think it was probably our great-grandfather. His mother died young. She was only 42.

How did you figure that out?

A lot of genealogy research.

So each of our great-great-grandmother's descendants could potentially have inherited the mutation?

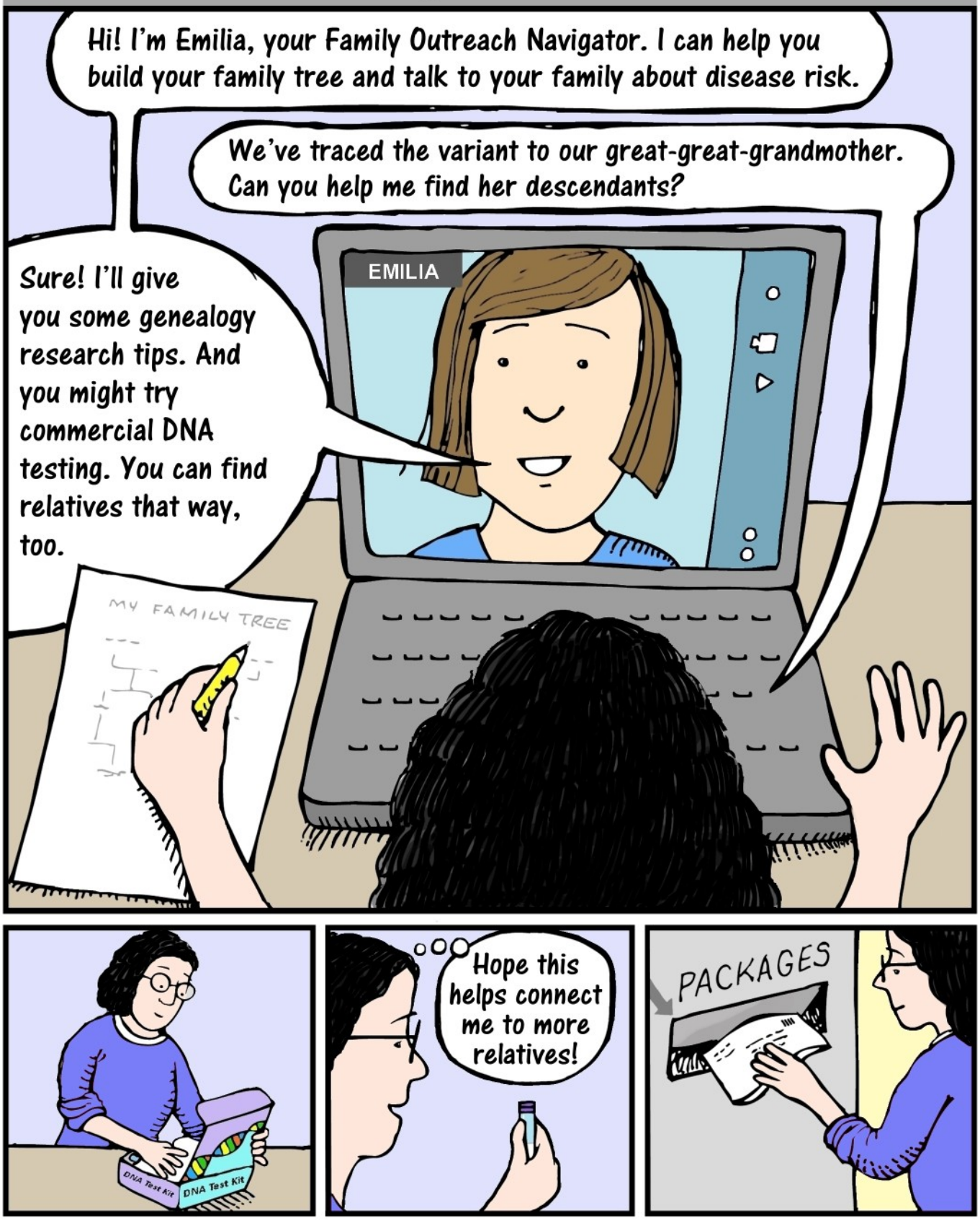
I'm trying to find as many of her descendants as possible. I want to warn them about the variant and tell them about genetic testing.

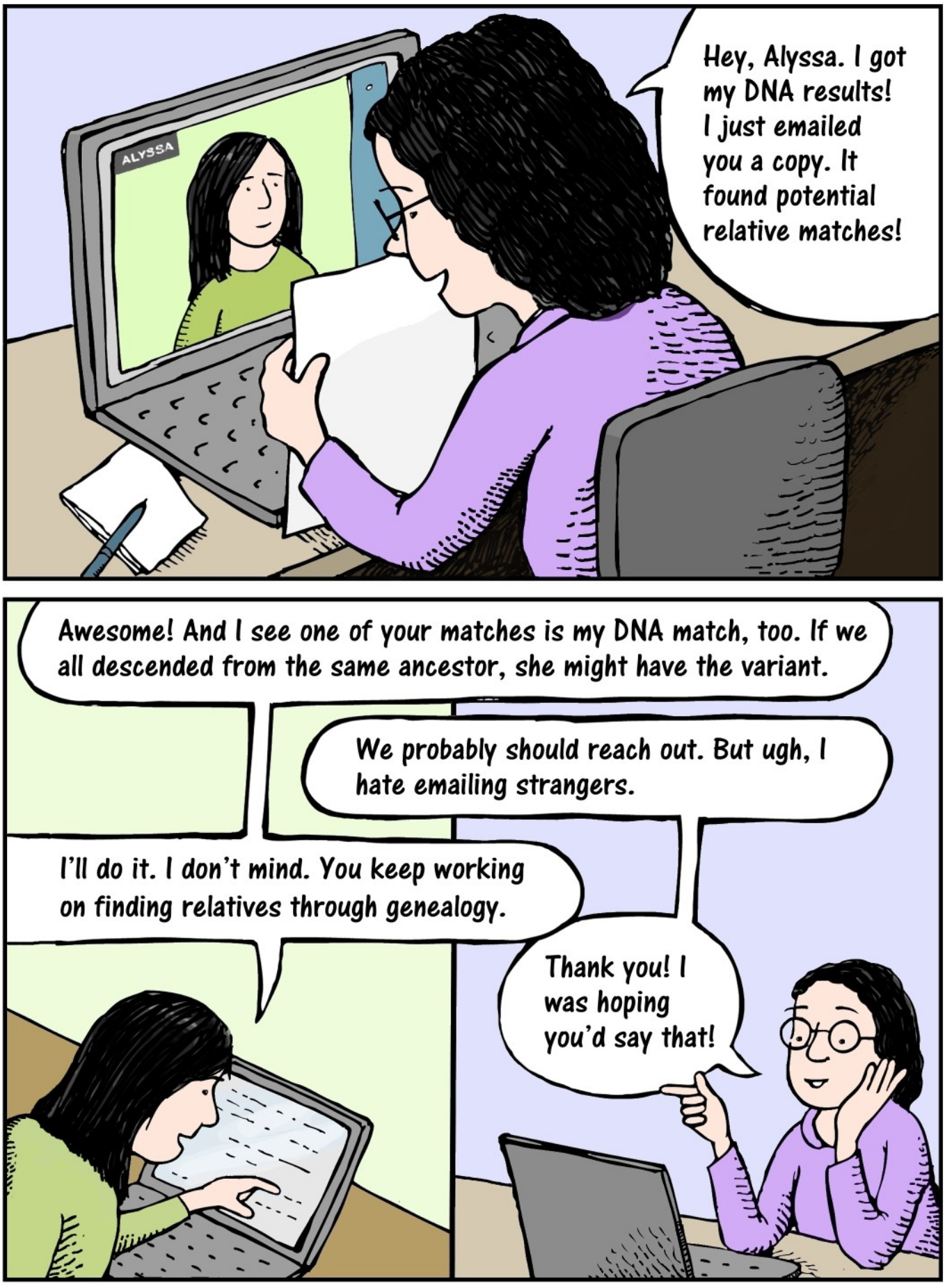
I don't know much about genealogy, but I'd really like to help.

Talk to Emilia, our ConnectMyVariant Family Outreach Navigator. She can get you started.

CHAPTER THREE

Connecting the Generations




ALYSSA
Hey, Alyssa. I got my DNA results! I just emailed you a copy. It found potential relative matches!
Awesome! And I see one of your matches is my DNA match, too. If we all descended from the same ancestor, she might have the variant.
We probably should reach out. But ugh, I hate emailing strangers.
I'll do it. I don't mind. You keep working on finding relatives through genealogy.
Thank you! I was hoping you'd say that!

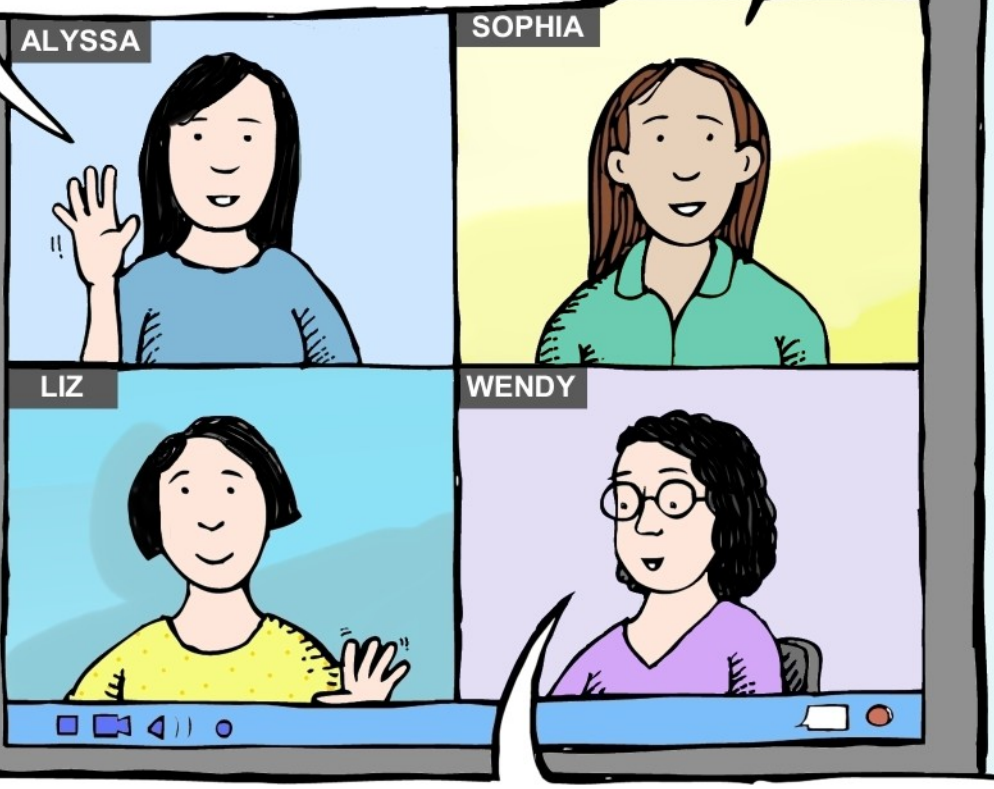
A couple months later...

Welcome, Sophia. It's great to finally meet you after our DNA matched.

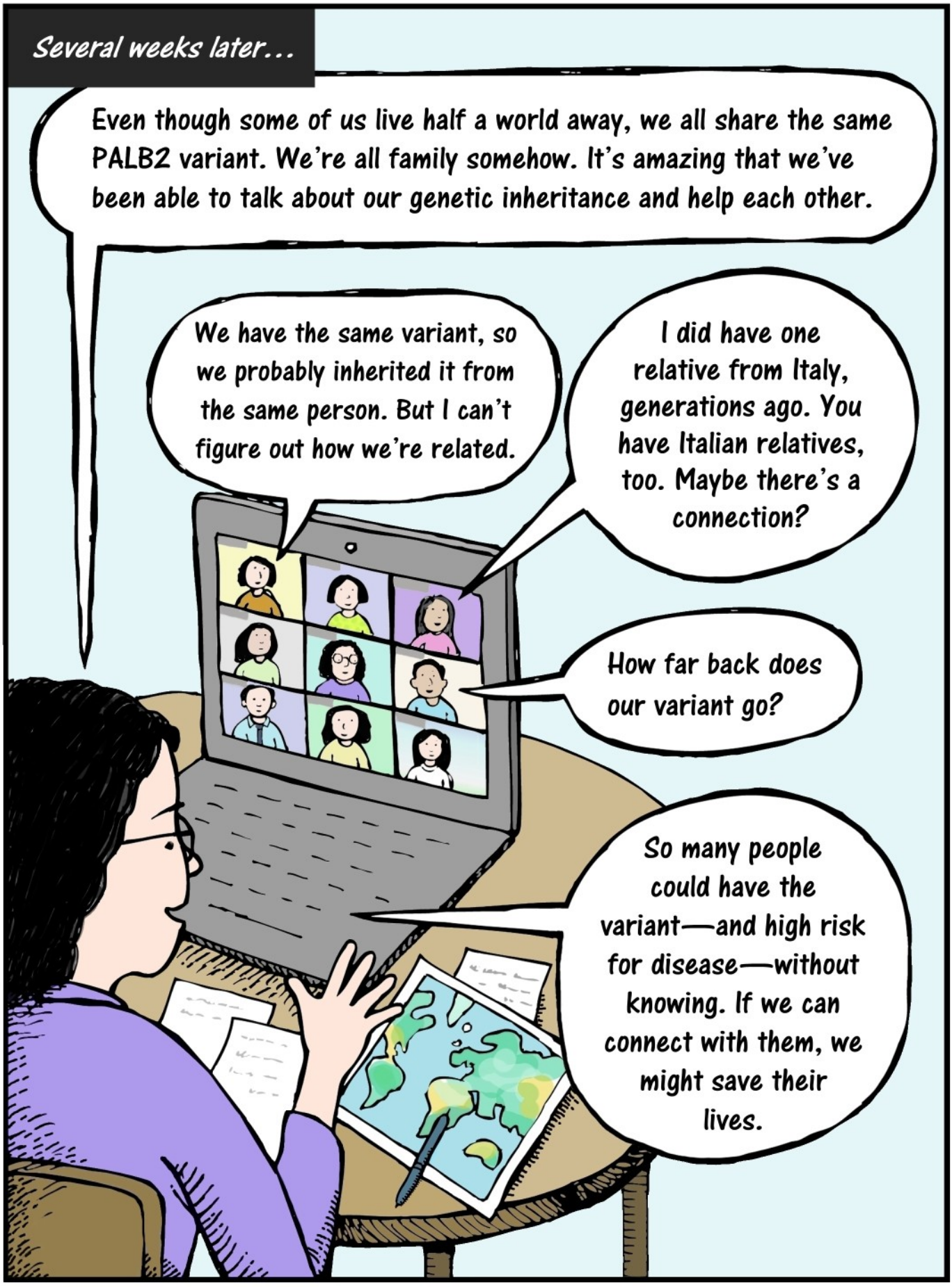
I never knew I had fourth cousins until a couple months ago!

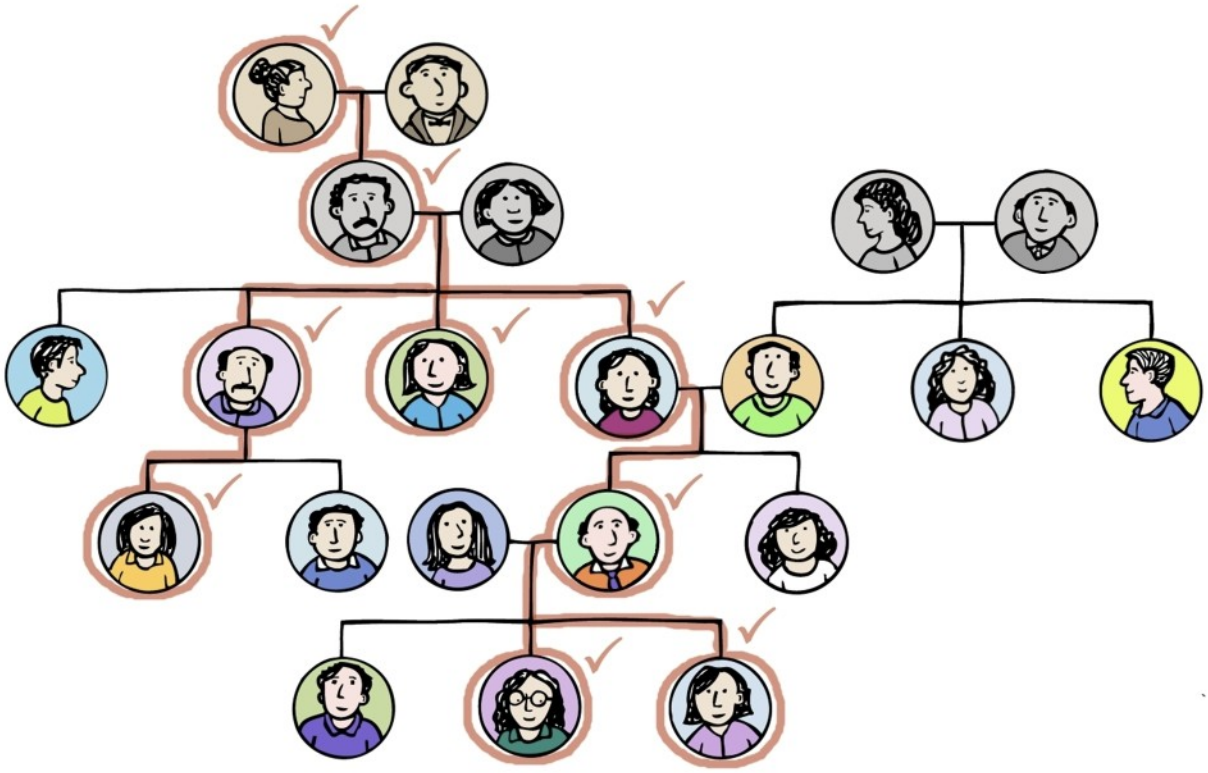
I would never have gotten genetic testing if you hadn't reached out. Now I know I have the variant, I'm getting preventative surgery. You saved my life!

And you helped us trace the variant back one more generation. Since you descended from our great-great-grandmother's mother, we know her other descendants might have the variant, too.



Did you all see that another person signed up for ConnectMyVariant with our variant? Maybe he's one of our fourth cousins, too. Let's invite him to our group. We can grow our circle to help spread the word.


Several weeks later...
Even though some of us live half a world away, we all share the same PALB2 variant. We're all family somehow. It's amazing that we've been able to talk about our genetic inheritance and help each other.
We have the same variant, so we probably inherited it from the same person. But I can't figure out how we're related.
I did have one relative from Italy, generations ago. You have Italian relatives, too. Maybe there's a connection?
How far back does our variant go?
So many people could have the variant—and high risk for disease—without knowing. If we can connect with them, we might save their lives.



If you or someone in your family has been diagnosed with an inherited pathogenic variant, you can build a family history to figure out which of your relatives are also at risk.

When you find out which grandparent had the variant, you reveal which of your cousins could have inherited it. When you find out which great-grandparent had the variant, you reveal which of your second cousins could have inherited it.

As you identify relatives who may have the variant, you can encourage them to get genetic testing. This simple act could save their lives.

The further back you trace your family tree, the more people you can help.

If you meet people outside your close family who have the same variant as you, they are probably your distant relatives. Most people with the same variant inherited it from a common ancestor. Build a team with them. Share your family trees. Look for the same surnames or geographic locations in your trees—these are hints about where branches might connect. Linking family trees could take months or years, but every new branch connected to your tree reveals more people who may have the mutation. You can warn them about the variant so they can talk to their doctors.

It's more than cascade testing. It's **snowball testing**. Like a rolling snowball, the number of people who know about the variant grows bigger and bigger. One person becomes two, and two becomes four, and four becomes eight, and so on. The team works together to tell more and more distant relatives while they can still prevent disease.

Ready to get the snowball rolling?

Visit

www.ConnectMyVariant.org

for

- ✓ *Opportunities to connect with others like you.*
- ✓ *Resources to help you build your family tree and your family's disease history.*
- ✓ *Resources to help you talk to your family about inherited disease.*

ConnectMyVariant's Mission:

To end hereditary disease by bringing families together.

“When I signed up for ConnectMyVariant, it was even better than I hoped. Every patient should have access to this level of support for family outreach.”

— Michelle Springer, MS, Certified Genetic Counselor

Prevention through Connection

Connect with relatives.
Reduce inherited disease risk.

ConnectMyVariant is an innovative nonprofit that builds communities dedicated to communication with relatives about genetic testing and hereditary disease prevention.

Find us at ConnectMyVariant.org.

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